NOVARTIS

Global Clinical Development - General Medicine

Secukinumab (AIN457)

Clinical Trial Protocol [CAIN457F2342] / NCT02404350

A Phase III, randomized, double-blind, placebo controlled multi-center study of subcutaneous secukinumab (150 mg and 300 mg) in prefilled syringe to demonstrate efficacy (including inhibition of structural damage), safety, and tolerability up to 2 years in subjects with active psoriatic arthritis (FUTURE 5)

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List of abbreviations

ACR	American College of Rheumatology
AE	Adverse event
ALT/SGPT	Alanine aminotransferase/serum glutamic pyruvic transaminase
ANA	Antinuclear antibody
Anti-CCP	Anti-cyclic citrullinated peptide
Anti-dsDNA	Anti-double stranded DNA antibodies
AS	Ankylosing Spondylitis
AST/SGOT	Aspartate aminotransferase/serum glutamic oxaloacetic transaminase BDR Bionanalytical Data Report
BSA	Body Surface Area
BSL	Baseline
CASPAR	ClASsification criteria for Psoriatic ARthritis
CFR	Code of Federal Regulations (US)
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
DAS	Disease Activity Score
DLQI	Dermatology Life Quality Index
DMARD	Disease Modifying Antirheumatic Drug
DNA	Deoxyribonucleic acid
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
EMA/EMEA	European Medicines (Evaluation) Agency
[redacted]	[redacted]
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
[redacted]	[redacted]
FAS	Full Analysis Set

FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI©	Health Assessment Questionnaire – Disability Index
HIV	Human immunodeficiency virus
HRQoL	Health-related Quality of Life
hsCRP	High sensitivity C-Reactive Protein
IB	Investigator Brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
[redacted]	
IIS	Integrated Information Sciences
IL	Interleukin
IR	inadequate responder
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	IntraUterine Device
IUS	IntraUterine System
i.v.	intravenous(ly)
IVR	Interactive Voice Response
[redacted]	[redacted]
[redacted]	[redacted]
LFT	Liver function test (raised serum transaminases and/or bilirubin levels)
LLOQ	Lower Limit of quantification
MAR	Missing at Random Assumption
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical dictionary for regulatory activities
[redacted]	[redacted]
mmHg	Millimeter mercury
MMRM	Mixed-effects repeated measures model
MRI	Magnetic resonance imaging

MTX	Methotrexate
NR	non-responder
NSAID	Non-steroidal anti-inflammatory drug
[redacted]	[redacted]
PASI	Psoriasis Area and Severity Index
PCS	Physical Component Summary
PFS	Prefilled syringe
[redacted]	[redacted]
[redacted]	[redacted]
PoC	Proof of Concept
PPD	Purified protein derivative
PRN	*Pro re nata* (as required)
PRO	Patient Reported Outcome
PsA	Psoriatic arthritis
[redacted]	[redacted]
[redacted]	[redacted]
QoL	Quality of Life
RA	Rheumatoid arthritis
RBC	Red blood cell
RF	Rheumatoid factor
SAE	Serious adverse event
s.c.	Subcutaneous(ly)
SCR	Screening
[redacted]	[redacted]
SJC	Swollen Joint Count
SpA	Spondyloarthritis
SUSAR	Suspected Unexpected Serious Adverse Reactions
TJC	Tender Joint Count
TNF	Tumor necrosis factor
TNF-IR	TNFα Inhibitor Inadequate Responders
ULN	Upper limit of normal
VAS	Visual analog scale

WBC	White blood cell
WHO	World Health Organization
[redacted]	[redacted]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	Any drug (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the drug being tested in the trial
DMARD	Disease Modifying Anti-rheumatic Drug; in this study this term refers only to non-biologics
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Escape treatment	In this study this is reserved for the switch from placebo treatment to active study treatment in case of non-response. The subject remains active in the trial
Inadequate response to TNFα	Active disease despite stable treatment with anti-tumor necrosis factor α (TNFα) for at least 3 months at a stable dose or for at least one dose in the case of lack of tolerance
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US Code of Federal Regulation (CFR) 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This *includes* any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally *does not include* protocol-specified concomitant background therapies when these are standard treatments in that indication
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an Interactive Response Technology (IRT) system
Mis-Randomization	A subject who is randomized to a treatment group, but did not receive any study treatment
Non-responder	A subject with <20% improvement from baseline (BSL) in either tender joint count (TJC) or swollen joint counts (SJC)
Period/Epoch	The planned stage of the subjects’ participation in the study. Each period serves a purpose in the study as a whole. Typical periods are: determination of subject eligibility, wash-out of previous treatments, exposure of subject to treatment or to follow-up on subjects after treatment has ended. Study ‘epoch’ will be referred to study period in the protocol
Protocol	A written account of all the procedures to be followed in a trial, which describes all the administrative, documentation, analytical and clinical processes used in the trial.
Premature subject/patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all study treatment administration and/or assessments; at this time all study treatment administration is discontinued and no further assessments are planned, unless the patient will be followed for progression and/or survival

Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Re-Screening	A subject who qualified for all or most eligibility criteria but could not be randomized within the screening period can be considered for re-screening only once
Rescue medication	Any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening/ exacerbation of their disease
Responder	A subject with ≥20% improvement from BSL in both tender joint count (TJC) and swollen joint counts (SJC)
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Subject Number	A number assigned to each patient who enrolls into the study
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study

Amendment 2

Amendment rationale

This protocol amendment is issued to correct formatting and typographical errors in Amendment 1 to increase clarity and consistency of the text.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol will not require IRB/IEC approval prior to implementation.

The changes herein do not affect the Informed Consent.

Amendment 1

Amendment rationale

This protocol amendment is issued for the following reasons:

1. **To allow dose escalation of secukinumab administered sc every 4 weeks from 150 mg to 300 mg beginning at the Week 52 visit**.

Phase 3 studies in subjects with active PsA (CAIN457F2306 and CAIN457F2312) demonstrated the superior efficacy of secukinumab 150 mg sc (both studies) and 300 mg sc (300mg arm in CAIN457F2312 only) regimens over placebo. Secukinumab 150 mg sc and 300 mg sc regimens had a rapid onset of response and similar magnitude of efficacy across several endpoints.

While secukinumab 150 mg sc and 300 mg sc regimens are both more efficacious than placebo regardless of TNFα-inhibitor (TNF-IR) status, the 300 mg sc regimen provided the greatest efficacy across multiple PsA domains including ACR20, ACR50, ACR70, HAQ-DI, PASI 75, PASI 90, SF-36 PCS, and presence of dactylitis and enthesitis in TNF-IR patients.

Evidence of dose response was shown in TNF-IR patients favoring secukinumab 300 mg sc over 150 mg sc at the Week 24 efficacy endpoint used for the primary and secondary efficacy analyses of CAIN457F2312. Indeed, ACR20/50/70 response rates at Week 24 in TNF-IR patients were higher with secukinumab 300 mg sc compared to 150 mg sc (45.5% vs 29.7%, 27.3% vs 18.9%% and 15.2% vs 10.8% respectively). This trend was maintained up to week 52.

Furthermore, secukinumab 300 mg sc was more efficacious than 150 mg sc in achieving clinically meaningful improvements in skin disease, particularly with respect to clear/almost clear skin (PASI 90, IGA mod 2011 0/1) in subjects with moderate to severe psoriasis (defined as ≥ 10% BSA). There was a clear dose response favoring secukinumab 300 mg sc in the higher thresholds of skin clearance. The difference between 300 mg sc and 150 mg sc regimens was more pronounced in the more difficult-to-achieve PASI 90 and IGA mod 2011 0/1 endpoints, with 21.9% and 27.4% more patients with ≥ 10% BSA compared to 8.2% and 3.3% more patients with < 10 % BSA reaching PASI 90 and IGA mod 2011 0/1 responses, respectively, at Week 24. Therefore, secukinumab 300 mg sc afforded greater improvement in plaque psoriasis than 150 mg sc, particularly in the achievement of clear/almost clear skin, in subjects with moderate to severe psoriasis (≥ 10% BSA).

Thus, given the results outlined above, and in order to maintain a high proportion of clinically meaningful response without compromising the important Week 24 and Week 52 radiographic data integrity, the 150mg sc dose should be escalated to 300 mg sc every 4 weeks for subjects whose signs and symptoms are not well controlled, and may improve further with an increase in dose as judged by investigator beginning at Week 52. As treatment assignment will remain blinded until after the database is locked for the planned Week 52 interim analysis, for many subjects, both the decision to escalate and dose escalation will be performed in a blinded manner.

2. **Moving all clinical (primary and secondary) endpoints from Week 24 to Week 16 except x-ray endpoint (mTSS)**

In order to reflect the true placebo control portion of the study without need for extrapolation for week 16 non-responders, primary and secondary endpoints are changed from Week 24 to Week 16 except for x-ray endpoint (mTSS). Up to week 16, all patients will stay in the randomized study treatment regimen without switch or rescue. Therefore the comparison between treatment groups at week 16 is not affected by "rescue penalty".

3. Reordering the secondary endpoint hierarchy

An important purpose for this study is to investigate the x-ray data. Therefore the endpoint for x-ray data (mTSS) is moved up to the first family together with the primary endpoint ACR20. With the consideration of the importance of other efficacy endpoints for this protocol, the hierarchy of those endpoints is adjusted from more important to less important for this study in the secondary family.

4. Adding additional X-ray at Week 24 for patients who are non-responders at Week 16

In order to assess secukinumab's treatment effect on inhibiting the progression of joint/bone structural damage, comparison of the change from baseline at Week 24 in the modified sharp scores (mTSS) between active and placebo is required. To minimize a subject's duration on ineffective treatment, clinically non-responding patients (<20% reduction in their baseline active joint count) at Week 16 are switched to active secukinumab treatment in a blinded fashion. To maintain the blind, both the active and placebo patients have X-rays obtained at Week16 before their blinded treatment is changed. This allows for a comparison between placebo and secukinumab, but requires extrapolation of this data to Week 24 based on the change in mTSS observed between baseline and Week 16. This extrapolation requires a strong assumption that the subjects' score would have continued to change at exactly the same linear rate as observed from baseline to week 16. Based on prior PsA studies CAIN457F2306 and CAIN457F2312, approximately 66% of placebo and 33% of secukinumab subjects in the current study are expected to be a non-responder at Week 16 and have an X-ray obtained at that visit. Health authorities have expressed concern that for this subset of subjects, no real Week 24 radiographic data prior to this amendment had been planned and this large number of subjects are reliant on extrapolation of Week 16 data to Week 24 to assess secukinumab treatment effect. To address these concerns and to strengthen the extrapolation method, a Week 24 X-Ray is being added for this subset of subjects. This will lessen the number of patients without observed data *at Week 24* and substantially improve the understanding of the relationship of radiographic evidence of structural disease progression over time, especially between the Week 16 and Week 24 time frame. This additional information will be applied to the important supportive sensitivity analyses, some of which are predictive models built on relationships of radiographic structural changes over time. These added films will substantially increase the accuracy and justifiability of statistical analyses including both the primary and sensitivity analyses.

5. Update analysis for Joint/bone structural damage at Week 24 to account for the additional Week 24 X-ray for Week 16 non-responders

The primary analysis for total modified Sharp score is updated to include available X-ray assessments at Week 24 for secukinumab treated subjects who meet early escape criteria at Week 16. This is based on the following:

- The main purpose of this analysis is to compare treatment group difference **at Week 24** (change from baseline). Therefore, if data at Week 24 from the active treatment group is available, it should be used in the analysis.
- For placebo non-responders at Week 16 (i.e. rescued patients), the data at Week 24 are not reflective of their original randomized treatment due to the placebo non-responders having switched to secukinumab at Week 16. Thus, the "de-facto" ITT analysis that could be proposed in this setting would be difficult to interpret. This approach for the handling of the placebo non-responders as missing is consistent with what has been done for other continuous endpoints using an MMRM analysis. An analysis using the observed data at Week 24 for all early escaped subjects (including placebo subjects who switch to secukinumab at Week 16) is planned to be amongst other sensitivity analyses using valid missing data imputation methods.

6. Add a required wash-out period for Apremilast

At the time the protocol was written, Apremilast (Otezla ®) was not approved for treatment of PsA and a washout period prior to randomization was not included in the protocol. Consequently, a minimum four-week washout period for subjects who received Apremilast before randomization is added.

None of the changes made are due to evidence-based safety concerns.

At the time this amendment becomes effective, approximately 60% of the patients are estimated to have been randomized.

7. Introduce update Novartis standard language for SAEs reporting

New Novartis standard language for SAEs reporting is available and therefore introduced.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version using strike through red font for deletions and red underlined for insertions.

Additionally, this protocol amendment includes the correction of typographical errors, formatting errors and editorial changes to increase clarity and consistency of the text. Consequently changes were incorporated directly in the protocol with track changes, even if not listed specifically in this section.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/ Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Protocol summary

Protocol number	CAIN457F2342
Title	A Phase III, randomized, double-blind, placebo controlled multi-center study of subcutaneous secukinumab (150 mg and 300 mg) in prefilled syringe to demonstrate efficacy (including inhibition of structural damage), safety, and tolerability up to 2 years in subjects with active psoriatic arthritis (FUTURE 5)
Brief title	Study to demonstrate the efficacy (including inhibition of structural damage), safety and tolerability up to 2 years of secukinumab in Active Psoriatic Arthritis
Sponsor and Clinical Phase	Novartis Phase III
Investigation type	Drug; Biologic
Study type	Interventional
Purpose and rationale	The purpose of this study is to demonstrate efficacy including effect on inhibition of progression of structural damage, safety and tolerability up to 2 years with primary focus at Week 16 clinically and Week 24 radiographically, to support the use of secukinumab pre-filled syringe (PFS) by subcutaneous (s.c.) self-administration with or without loading regimen in subjects with active Psoriatic Arthritis (PsA) despite current or previous NSAID, DMARD therapy and/or previous anti-TNFα therapy. Long term efficacy up to 2 years will be based on signs and symptoms of joint/bone structure preservation (X-ray) and improvement in physical function measured by Health Assessment Questionnaire – Disability Index (HAQ-DI©), as well as skin and nail improvement for psoriasis signs.
Primary Objective(s)	To demonstrate that the efficacy of secukinumab 150 mg s.c. (with or without loading regimen) or 300 mg s.c. with loading regimen, at Week 16 is superior to placebo based on proportion of subjects achieving American College of Rheumatology 20 (ACR20) response in subjects with active PsA.
Secondary Objectives	To evaluate: 1. The change from baseline at Week 24 with secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) compared with placebo for **joint/bone structural damage (using van der Heijde modified total Sharp score (mTSS))**. 2. The efficacy of secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) at Week 16 compared with placebo based on the proportion of subjects achieving **Psoriatic Area and Severity Index 75 (PASI75)** response. 3. The efficacy of secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) at Week 16 compared with placebo based on the proportion of subjects achieving **Psoriatic Area and Severity Index 90 (PASI90)** response. 4. The efficacy of secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen), at Week 16 compared

	with placebo based on the proportion of subjects achieving an **ACR50** response. 5. The improvement on secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen), at Week 16 compared with placebo for the disease activity assessed by the changes in **HAQ-DI©** relative to baseline. 6. The improvement on secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) at Week 16 compared with placebo for the disease activity assessed by the changes in **Disease Activity Score for 28 joints C-Reactive Protein (DAS28-CRP)** (utilizing high sensitivity CRP (hsCRP)) relative to baseline. 7. The efficacy of secukinumab pooled regimen (150 mg with or without loading regimen, and 300 mg with loading regimen) at Week 16 compared with placebo based on the proportion of subjects with **enthesitis** in the subset of subjects who have enthesitis at BSL. 8. The efficacy of secukinumab pooled regimen (150 mg with or without loading regimen, and 300 mg with loading regimen) at Week 16 compared with placebo based on the proportion of subjects with **dactylitis** in the subset of subjects who have dactylitis at BSL. 9. Overall safety and tolerability of secukinumab.
Study design	This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design. A screening period (SCR) running up to 10 weeks before randomization will be used to assess subject eligibility followed by 104 weeks of treatment. At BSL approximately 990 subjects whose eligibility is confirmed will be randomized to one of four treatment groups in 2:2:2:3 ratio: • Group 1 - secukinumab 150 mg s.c. without loading regimen • Group 2 - secukinumab 150 mg s.c. with loading dose regimen • Group 3 - secukinumab 300 mg s.c. with loading dose regimen • Group 4 - Placebo s.c. **At randomization**, subjects will be stratified on the basis of previous anti-TNF therapy as TNFα inhibitor naïve (TNF-naïve) or TNFα inhibitor inadequate responders (TNF-IR). At each study treatment visit, one (for secukinumab 150 mg) or two (for secukinumab 300 mg) s.c. injections in the form of PFS will be administered, since secukinumab is available in 1.0 mL (150 mg) PFSs. Placebo to secukinumab is also available in 1.0 mL to match the active drug. **At Week 16**, subjects who have been randomized to secukinumab groups at BSL (Groups 1-3) will be classified as either responders (≥20% improvement from BSL in both tender joint count (TJC) and swollen joint counts (SJC)) or non-responders (<20% improvement from BSL TJC or SJC), however they will continue on the same treatment irrespective of their response status. **At Week 16**, subjects who have been randomized to placebo at BSL (Group 4) will be classified as either responders (≥20% improvement from BSL in both TJC and SJC) or non-responders (<20% improvement from BSL TJC or SJC):

	• Subjects who are **non-responders** will receive either secukinumab 150 mg or 300 mg s.c. every 4 weeks starting at Week 16 (as dictated by treatment sequence assigned to these subjects at BSL). • Subjects who are **responders** will continue to receive placebo every 4 weeks. Starting Week 24, these subjects will receive either secukinumab 150 mg s.c. or 300 mg s.c. every 4 weeks starting at Week 24 (as dictated by treatment sequence assigned to these subjects at BSL). **At Week 24**, subjects who are still receiving placebo s.c. injection will receive either secukinumab 150 mg s.c. or 300 mg s.c. every 4 weeks starting at Week 24 (as dictated by treatment sequence assigned to these subjects at BSL). **Beginning at Week 52,** for subjects whose signs and symptoms are not fully controlled, and who the investigator believes may improve further with an increase in dose, may have the secukinumab dose increased to 300mg s.c. every 4 weeks. This will be performed in a blinded manner until after the Week 52 interim analysis database lock is performed. **After the Week 52 database lock and analyses** have been completed, site personnel and subjects will be unblinded to the original randomized treatment (sequence) assignment at randomization. In addition, treatment will be given open-label in order to eliminate the placebo injection. The subject will continue to receive the same active dose of secukinumab as open-label treatment administered until Week 100.
Population	This is an international study and it is expected that approximately 990 subjects will be randomized. Subjects can be re-screened only once and no re-screening study related procedures should be performed prior to written re-consent by the subject. Mis-randomized subjects will not be re-screened. A screening failure rate of 20% and post-randomization dropout rate of 25% is anticipated in the first year. Enrollment will stop as soon as the target number and proportions of randomized subjects in the respective treatment group is reached.
Inclusion criteria	Subjects eligible for inclusion in this study have to fulfill **all** of the following criteria: • Diagnosis of PsA classified by ClASsification criteria for Psoriatic ARthritis (CASPAR) and with symptoms for at least 6 months with moderate to severe PsA who must have at BSL ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each). • Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at screening. • Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or a documented history of plaque psoriasis. • Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs.

	• Subjects who are regularly taking NSAIDs as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 24. • Subjects taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24. • Subjects taking methotrexate (MTX) (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 52.
Exclusion criteria	Subjects fulfilling any of the following criteria are not eligible for inclusion in this study: • Chest X-ray or chest magnetic resonance imaging (MRI) with evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified physician. • Subjects taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine). • Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor. • Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. • Subjects who have ever received biologic immunomodulating agents except for those targeting TNFα (investigational or approved). • Previous treatment with any cell-depleting therapies including but not limited to anti- CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti- CD19).
Investigational and reference therapy	Investigational treatment secukinumab 150 mg provided in 1ml Prefilled Syringe (PFS) Reference treatment: secukinumab placebo provided in a 1 ml PFS.

Efficacy assessments	• American College of Rheumatology (ACR) 20, 50 and 70 responses
	  • Swollen Joint Count (SJC)/Tender Joint Count (TJC)
	  • Patient's global assessment of disease activity (VAS)
	  • Physician's global assessment of disease activity (VAS)
	  • Patient's assessment of PsA pain intensity (VAS)
	  • Health Assessment Questionnaire – Disability Index (HAQ-DI©)
	  • high sensitivity C-Reactive Protein (hsCRP) and Erythrocyte Sedimentation Rate (ESR)
	• Progression of structural damage by X-ray (hands/wrists and feet) – van der Heijde mTSS and subscores (erosion and joint space narrowing score)
	• [redacted]

	• [redacted] • [redacted] • [redacted] • [redacted] • [redacted] Dactylitis [redacted] • [redacted] Enthesitis [redacted] • Psoriasis Area and Severity Index (PASI) • [redacted] • [redacted] • [redacted]
Safety assessments	• Evaluation of adverse events (AE)/SAE's • Physical examination • Vital signs • Height and weight • QuantiFERON TB-Gold test or Purified Protein Derivative (PPD) skin test • Electrocardiogram (ECG) • Local tolerability (Injection site reactions) • Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis) • Pregnancy and assessment of fertility • Tolerability of secukinumab • [redacted]
Other assessments	a. Quality of Life questionnaires/ Patient reported outcomes (PROs) b. [redacted] c. [redacted] d. [redacted]
Data analysis	The primary endpoint in the study is ACR20 at Week 16 for all subjects. Secondary objectives will be to compare secukinumab to placebo according to a sequential hierarchy testing procedure and include change from baseline in van der Heijde modified total Sharp score (Week 24), PASI75 and PASI90 response (Week 16), ACR50 response (Week16), change from baseline in HAQ-DI© (Week 16), change from baseline in DAS28-CRP (Week 16), presence of enthesitis, presence of dactylitis (Week 16). Safety analyses will include summaries of AEs, laboratory measurements, ECGs and vital signs.
Key words	Active Psoriatic Arthritis, subcutaneous, secukinumab in prefilled syringe

1 Introduction

1.1 Background

Psoriatic arthritis (PsA) is an immune-mediated chronic inflammatory disease belonging to the spectrum of conditions commonly referred to as spondyloarthritidies (SpA). While the various SpA may be diverse in their clinical presentations, common environmental as well as genetic factors associated with susceptibility to SpA are suspected (Turkiewicz and Moreland 2007). This latter notion was recently corroborated by findings in a large-scale single nucleotide polymorphism (SNP) scan study, where IL-23R variants that were previously linked to Crohn`s disease and psoriasis (diseases that may both co-exist with spondylarthritides) conferred risk to developing ankylosing spondylitis (AS) (Barrett et al 2008). Together, a common pathway including the IL-23/IL-17 axis may play a role in seronegative SpAs including PsA.

Psoriatic arthritis is a frequent chronic immune-mediated disease encompassing a spectrum of overlapping clinical entities (Moll and Wright 1973). About 10-40% of patients with psoriasis suffer from PsA. It is not only more common but also more severe than previously thought (Gladman 2004, Taylor et al 2006). PsA is associated with significant morbidity and disability, and thus constitutes a major socioeconomic burden. Typically diseases modifying anti-rheumatic drugs (DMARDs) are used for PsA including methotrexate (MTX), sulfasalazine, cyclosporine, and leflunomide, however, these are often inadequate because they only partially control established disease (Mease 2008).

Several lines of evidence support the notion of prominent T cell involvement in the pathogenesis of PsA. Memory CD4+ and CD8+ cells are present in skin lesions as well as the inflamed synovium that express activation markers and have characteristics of oligoclonal expansion. (Curran et al 2004; Tassiulas et al 1999) Clinical trials demonstrated efficacy of T cell targeted therapy in PsA (cyclosporine A, CTLA4 Ig, alefacept). TNF blocking therapy was successfully introduced to the treatment of patients with PsA (Mease et al 2000). Despite these efforts, an unmet clinical need exists for patients with PsA for better disease control and long term prevention of structural damage beyond mere abrogation of inflammatory processes.

IL-17 antagonism represents a novel therapeutic approach aimed at interference with the chronic inflammatory process by selectively targeting the predominant proinflammatory cytokine of the helper T17 cell subset. Additional effects of anti-IL-17 on bone homoeostasis via RANKL and IL-1, upstream of TNFα, can be inferred from animal studies (Koenders et al 2005). Assuming a potential role of IL-17 cells in the inflammatory infiltrate in PsA, it can be speculated that locally disturbed homeostasis of osteoclastogenic and osteoblastogenic mechanisms characteristic of PsA might be affected by IL-17 blockade, thus, potentially providing a therapeutic advancement to prevent structural damage in PsA.

Secukinumab (AIN457) is a high-affinity fully human monoclonal anti-human antibody that neutralizes IL-17A activity. IL-17A is the key cytokine in the newly discovered Th17 pathway which is thought to be an important mediator of autoimmunity. Neutralization of IL-17A has strong pre-clinical and clinical target validation and documentation of efficacy in a proof-of-concept study conducted in patients with PsA (CAIN457A2206) suggesting a clinically meaningful response for signs and symptoms up to Week 16. The efficacy of secukinumab in PsA patients is further supported by positive results for signs and symptoms (i.e. ACR20/50,

PASI75/90), resolution of dactilytis, enthesitis and inhibition of radiologic damage at Week 24 obtained in a phase III study (CAIN457F2306; N=606) employing an intravenous (i.v.) loading regimen (3x10 mg/kg) of secukinumab Q2W followed by secukinumab s.c. 75 mg or 150 mg administered Q4W. In another phase III study (CAIN457F2312; N=397) secukinumab also demonstrated positive efficacy results superior to placebo in patients with PsA through most components of the arthritic and skin measures of signs and symptoms and physical function in a population comprised of 65% naïve to TNF-α inhibitors and 35% patients who were inadequate responders to a TNF-α inhibitor. Therefore, treatment with secukinumab may also reduce loss of cartilage and erosion of bone in PsA and may result in improvement of symptoms and functional joint manifestations in afflicted patients.

As of 12-Jul-2014, approximately 10900 healthy subjects and patients have been enrolled into the secukinumab clinical program, of which approximately 8600 healthy subjects and patients have received at least one dose of secukinumab. Overall, patients have received secukinumab across various indications (RA, AS, PsA, psoriasis, multiple sclerosis, uveitis, Crohn's disease, dry eye, polymyalgia rheumatica) at doses ranging from single and multiple doses of 0.1 mg/kg to 30 mg/kg i.v. and 25 mg to 300 mg s.c. Full safety results from all PsA, AS and psoriasis completed studies show that secukinumab generally is safe and well tolerated. Please refer to the Investigator Brochure (IB) for a more detailed review of the pre-clinical and clinical information on secukinumab.

So far only one study (CAIN457F2306) has assessed the effect of secukinumab on progression of joint/bone structural changes. Further, this study (CAIN457F2306) did not include secukinumab 300 mg dose regimen and also did not study effect of loading dose vs. no load. This study is planned to confirm the utility (efficacy/safety) of secukinumab 150 mg s.c. and 300 mg s.c. dose regimens administered for 24 weeks including the efficacy in preventing the progression of active PsA (joint/bone structural changes), as assessed by radiographic methods when compared with placebo.

1.2 Purpose

The purpose of this study is to demonstrate efficacy, including the effect on inhibition of progression of structural damage, safety and tolerability of secukinumab for up to 2 years with a primary focus at Week 16 clinically and Week 24 radiographically, to support the use of secukinumab pre-filled syringes (PFS) by subcutaneous (s.c.) self-administration with or without loading regimen in subjects with active Psoriatic Arthritis (PsA) despite current or previous NSAID, DMARD therapy and/or previous anti-TNFα therapy. Long term efficacy of secukinumab for up to 2 years will be based on signs and symptoms of joint/bone structure preservation (X-ray) and improvement in physical function (HAQ-DI©), as well as skin and nail improvement for psoriasis signs.

[redacted]

2 Study objectives

2.1 Primary objective

To demonstrate that the efficacy of secukinumab 150 mg s.c. (with or without loading regimen), or 300 mg s.c. with loading regimen, at Week 16 is superior to placebo based on proportion of subjects with active PsA achieving American College of Rheumatology 20 (ACR20) response.

2.2 Secondary objectives

To evaluate:

1. The change from baseline to Week 24 with secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) compared with placebo for **joint/bone structural damage (using van der Heijde modified total Sharp score (mTSS))**.
2. The efficacy of secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) at Week 16 compared with placebo based on the proportion of subjects achieving **Psoriatic Area and Severity Index 75 (PASI75)** response.
3. The efficacy of secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) at Week 16 compared with placebo based on the proportion of subjects achieving **Psoriatic Area and Severity Index 90 (PASI90)** response.
4. The efficacy of secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen), at Week 16 compared with placebo based on the proportion of subjects achieving an **ACR50** response.
5. The improvement on secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen), at Week 16 compared with placebo for the disease activity assessed by the changes in HAQ-DI© relative to baseline.
6. The improvement on secukinumab 150 mg (with or without loading regimen), or 300 mg (with loading regimen) at Week 16 compared with placebo for the disease activity assessed by the changes in **Disease Activity Score for 28 joints (DAS28-CRP)** (utilizing hsCRP) relative to baseline.
7. The efficacy of secukinumab pooled regimen (150 mg with or without loading regimen, and 300 mg with loading regimen) at Week 16 compared with placebo based on the proportion of subjects with **enthesitis** in the subset of subjects who have enthesitis at baseline (BSL) .
8. The efficacy of secukinumab pooled regimen (150 mg with or without loading regimen, and 300 mg with loading regimen) at Week 16 compared with placebo based on the proportion of subjects with **dactylitis** in the subset of subjects who have dactylitis at BSL.
9. Overall safety and tolerability of secukinumab.

3 Investigational plan

3.1 Study design

This multicenter study uses a randomized, double-blind, placebo-controlled, parallel-group design. A screening period (SCR) running up to 10 weeks before randomization will be used to assess subject eligibility followed by 104 weeks of treatment.

At Baseline (BSL), approximately 990 subjects whose eligibility is confirmed will be randomized to one of four treatment groups in 2:2:2:3 ratio (The unbalanced ratio is adopted to improve the efficiency in the statistical test of the structural endpoint because the placebo population has higher variation. Overall ratio between active treatment and placebo is 2:1):

- Group 1 - secukinumab 150 mg s.c. without loading regimen:
  secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) administered at BSL, placebo (2 x 1.0 mL PFS) administered on Weeks 1, 2 and 3,

followed by secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) dosing every four weeks starting at Week 4.

- Group 2 - secukinumab 150 mg s.c. with loading dose regimen:
  secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4.
- Group 3 - secukinumab 300 mg s.c. with loading dose regimen:
  secukinumab 300 mg (2 x 1.0 mL PFS of 150 mg dose) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4.
- Group 4 - placebo s.c.:
  Placebo (2 x 1.0 mL PFS) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4. Note that Group 4 is split into two treatment arms based on the active treatment the subject will receive at Week 16/24 (described in detail in Section 5.2)

At randomization, subjects will be stratified on the basis of previous anti-TNF therapy as TNFα inhibitor naïve (TNF-naïve) or TNFα inhibitor inadequate responders (TNF-IR). The enrollment targets will be to have 70% for TNFα inhibitor naïve and 30% for TNF-IR (approximately 154:154:154:231 subjects are TNFα inhibitor naïve in each treatment groups) to ensure a representative subject population for the assessment of efficacy and safety.

Subjects in Group 4 (Placebo) will be randomized (1:1) at BSL to two different treatment sequences:

- Placebo s.c. till Week 16/24 followed by secukinumab 150 mg s.c. every 4 weeks starting at Week 16/24.
- Placebo s.c. till Week 16/24 followed by secukinumab 300 mg s.c. every 4 weeks starting at Week 16/24.

At each study treatment visit, one (for secukinumab 150 mg) or two (for secukinumab 300 mg) s.c. injections in the form of PFS will be administered, since secukinumab is available in 1.0 mL (150 mg) PFSs. Placebo to secukinumab is also available in 1.0 mL to match the active drug (see Section 5).

At Week 16, subjects who have been randomized to secukinumab groups at BSL (Groups 1-3) will be classified as either responders (≥20% improvement from BSL in both tender joint count (TJC) and swollen joint counts (SJC)) or non-responders (<20% improvement from BSL TJC or SJC), however they will continue on the same treatment irrespective of their response status.

At Week 16, subjects who have been randomized to placebo at BSL (Group 4) will be classified as either responders (≥20% improvement from BSL in both TJC and SJC) or non-responders (<20% improvement from BSL in TJC or SJC):

- Subjects who are **non-responders** will receive either secukinumab 150 mg or 300 mg s.c. every 4 weeks starting at Week 16 (as dictated by treatment sequence assigned to these subjects at BSL).

- Subjects who are **responders** will continue to receive placebo every 4 weeks. Starting at Week 24, these subjects will receive either secukinumab 150 mg s.c. or 300 mg s.c. every 4 weeks (as dictated by treatment sequence assigned to these subjects at BSL).

At Week 24, the assessments will be performed as described in Table 6-1. As described above, subjects who are still receiving placebo s.c. injection will receive either secukinumab 150 mg s.c. or 300 mg s.c. every 4 weeks starting at Week 24 (as dictated by treatment sequence assigned to these subjects at BSL).

Beginning at Week 52, for subjects whose signs and symptoms are not well controlled, and who the investigator believes may improve further with an increase in dose, may have the secukinumab dose increased to 300 mg s.c. every 4 weeks. This will be performed in a blinded manner until after the Week 52 interim analysis database lock is performed.

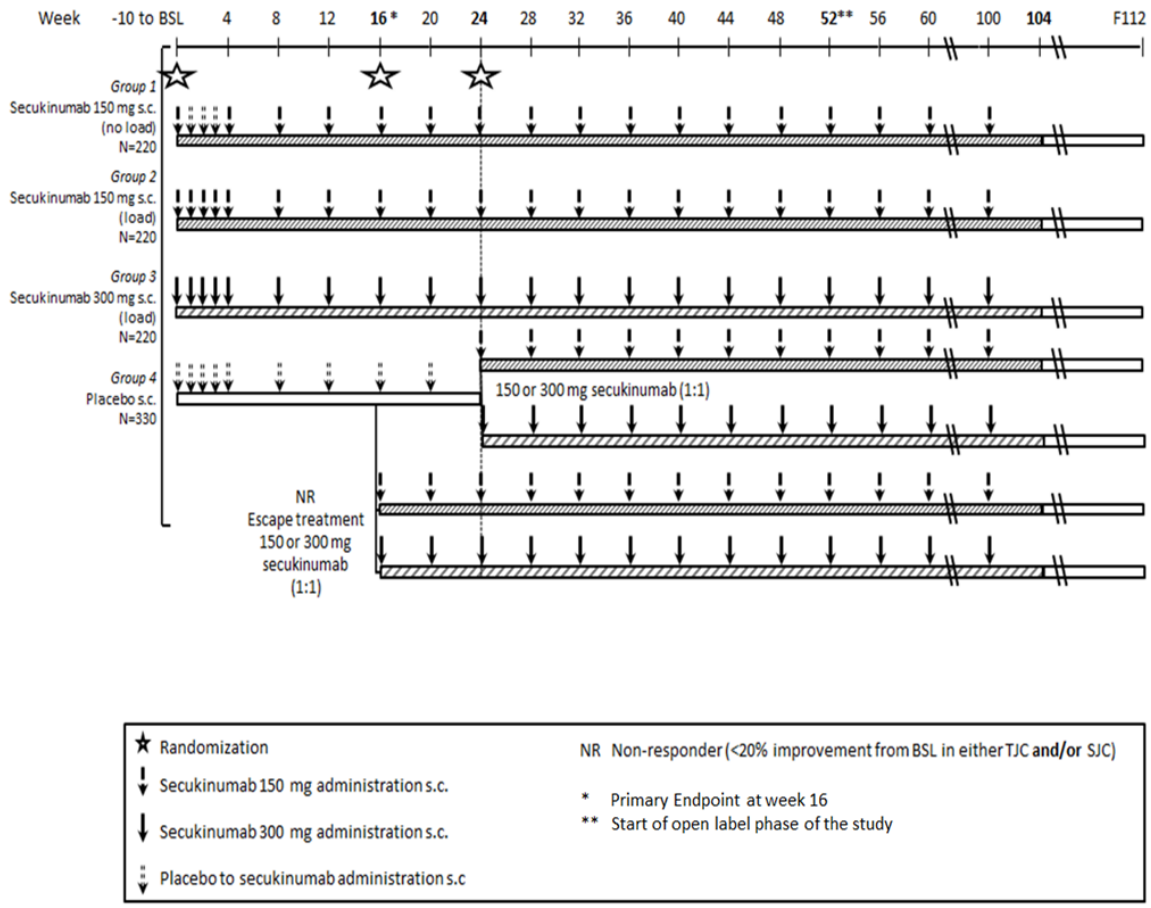
After the Week 52 database lock and analyses have been completed, site personnel and subjects will be unblinded to the original randomized treatment (sequence) assignment at randomization. In addition, treatment will be given open-label in order to eliminate the placebo injection (i.e., only 150 mg or 300 mg secukinumab will be dispensed as 1 or 2 PFS, respectively). The subject will continue to receive the same active dose of secukinumab as open-label treatment, administered until Week 100. Subjects will no longer receive the placebo PFS, which was administered to maintain blinding.

Rescue medication will not be allowed before the completion of Week 24 assessments (Section 5.5.6). Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited biologics (as described in Section 5.5.8) occurs prior to completion of Week 24 assessments, subjects will be discontinued from the study and will enter into the follow-up period after an End of Study visit. Efficacy will be assessed in detail at every study visit, and subjects who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator, or for any reason of their own accord, will be free to discontinue participation in the study at any time.

A follow-up visit is to be done 12 weeks after last study treatment administration for all subjects, regardless of whether they complete the entire study as planned or discontinue prematurely.

The total combined duration of treatment for this Phase III study is 2 years. Therefore, this study may be affected by agency review or potential product approval considerations. Whereby if the product is approved during study conduct, treatment groups in this proposed trial may be amended (via a protocol amendment) based on eventual agency recommendations for product usage in this indication.

Figure 3-1 Study design



3.2 Rationale of study design

The double-blind, randomized, parallel-group placebo controlled design used in this study up to Week 24 is in alignment with phase III trials of other biologics in this disease area and in compliance with the European Medicines (Evaluation) Agency (EMA/EMEA) guidelines (EMA 2006). Treatment duration in the placebo group is kept to a minimum. Placebo non-responders will start receiving active treatment at Week 16 and the placebo responders will start receiving active treatment at Week 24 to enable similar duration efficacy comparisons to other secukinumab PsA trials. Treatment data up to 2 years is being generated to demonstrate long-term efficacy and to support the safety data in this population.

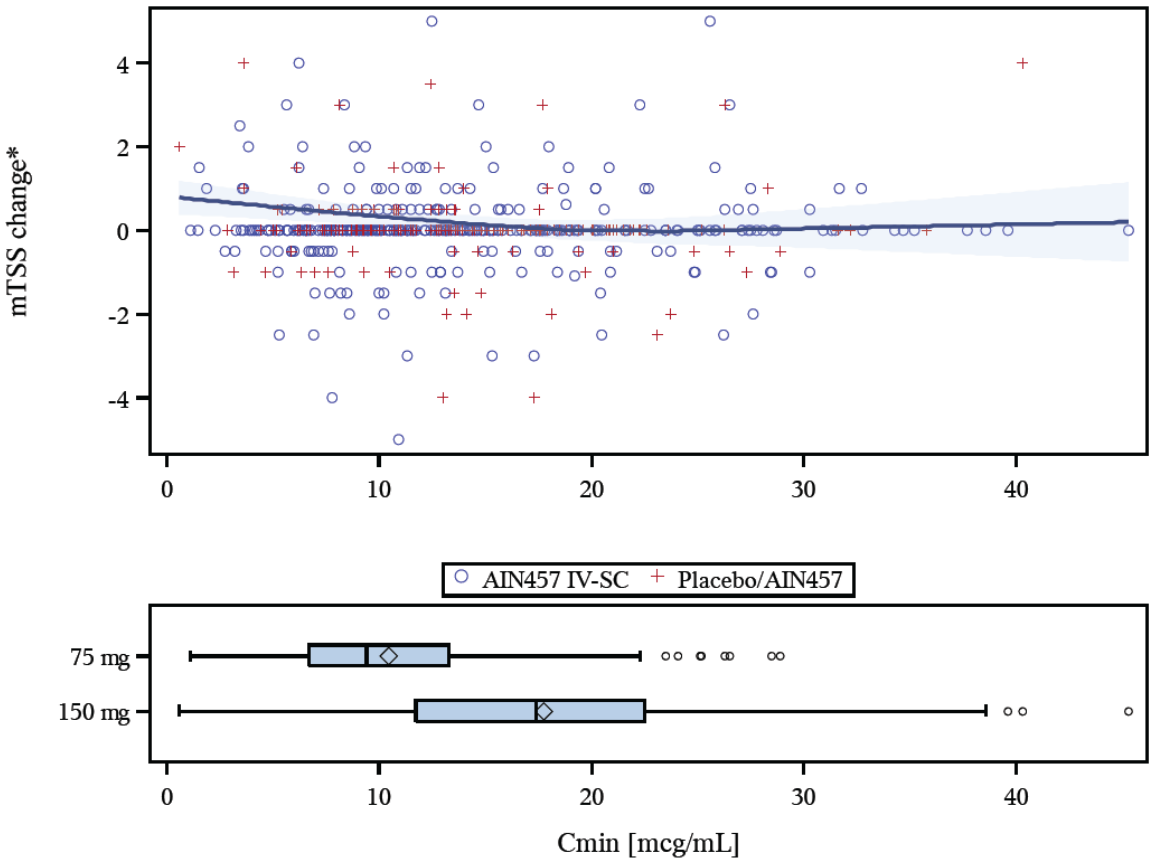
3.3 Rationale of dose/regimen, route of administration and duration of treatment

The dosing regimens in this study rely upon dose-efficacy relationships observed in a proof of concept (PoC) trial (CAIN457A2206) and two phase III trials (CAIN457F2306, CAIN457F2312) in PsA, as described below. The PoC trial in PsA (CAIN457A2206) suggested that after two i.v. secukinumab doses of 10 mg/kg given 3 weeks apart, secukinumab demonstrated high efficacy, achieving an ACR 20 response at Week 6 in 62% of the TNF-naïve

subjects on secukinumab vs. 20% on placebo, and was well-tolerated (McInnes et al 2013). The ongoing trials in PsA, CAIN457F2306 assessed the efficacy of both 75 mg and 150 mg s.c. maintenance doses (every 4 weeks) after loading regimens consisting of 3 i.v. doses of 10 mg/kg given at BSL, Weeks 2 and 4, and CAIN457F2312 assessed the efficacy of 75 mg, 150 mg and 300 mg s.c. maintenance doses (every 4 weeks) after loading regimens consisting of s.c. doses of 75 mg, 150 mg or 300 mg given at BSL, Weeks 1, 2, and 3. Given the similarity of the ACR 20 response seen at the Week 24 primary endpoint for the 150 mg dose in each of these studies, regardless of whether the loading dosing was i.v. (CAIN457F2306: 50.0% for 150 mg vs 17.3% for placebo) or s.c. (CAIN457F2312: 51.0% for 150 mg vs 15.3% for placebo), 150 mg is a sufficient dose to provide clinically and statistically significant efficacy, whereas higher loading doses of secukinumab do not appear to confer a greater response on the primary endpoint of ACR 20 at Week 24. In Study CAIN457F2312, PASI75 and PASI90 response was assessed in the subgroup of patients who had ≥ 3% skin involvement with psoriasis at BSL. For both PASI75 and PASI90 response rates, the difference to placebo at Week 24 was statistically significant for the secukinumab 150 mg and 300 mg doses (PASI75: 48.3%, $p = 0.0006$ and 63.4%, $p < 0.0001$; PASI90: 32.8%, $p = 0.0029$ and 48.8%, $p = 0.0002$, respectively). The percentage of responders increased as secukinumab dose increased, with the secukinumab 300 mg dose demonstrating a meaningful improvement over the secukinumab 150 mg dose (treatment differences between secukinumab 300 mg and 150 mg for PASI75 and PASI90 were 15.1% and 16%, respectively). Of note, the 75 mg s.c. loading/s.c. maintenance regimen tested in CAIN457F2312 achieved a statistically significant but clinically lower effect size in ACR 20 response of 29.3% and did not achieve statistically significant improvements in any of the efficacy endpoints tested in a pre-defined testing hierarchy, including PASI75, PASI90 DAS28 CRP, SF36 PCS, HAQ-DI©, ACR 50, dactylitis and enthesitis.

The effect of secukinumab on progression of bone/joint structural changes was studied at 75 mg and 150 mg maintenance doses in earlier study (CAIN457F2306). A graphical analysis of the changes in PsA mTSS over 52 weeks compared to the exposure shows a likelihood of radiographic progression in patients with low exposure (<15 mcg/mL) of 27% vs. an 18% radiographic progression in exposure of > 15 mcg/mL. This analysis demonstrates that a maintenance dose of 150 mg provides adequate exposure that result in long term inhibition of structural damage assessed by radiography as illustrated by the boxplots of minimum concentrations (Cmin) at the bottom of Figure 3-2.

Figure 3-2 Secukinumab progression of structural damage (van der Heijde modified total Sharp score) exposure-response relationship Week16/24 to 52 (Study CAIN457F2306)



* change with time (weeks) from baseline for AIN457 i.v.-s.c. arms; change from Week 16 for placebo non-responders; change from Week 24 for placebo responders

Source: [CAIN457F2306] data on file.

However, progression of bone/joint structural changes was not studied in study CAIN457A2312 and hence there is no previous study evaluating 300 mg s.c. dose on progression of bone/joint structural changes. Based on the exposure response analysis from CAIN457F2306 described above, this study will also assess if 300 mg s.c. dose would have better efficacy than 150 mg dose regimen.

This study is evaluating the secukinumab 150 mg s.c. dose with or without loading regimen and 300 mg s.c. dose with loading regimen for the treatment of adults with active PsA. The current trial is a phase III trial to assess the superiority of secukinumab 150 mg s.c. with or without loading regimen or 300 mg s.c. with loading regimen vs. placebo in patients with active PsA.

This study employs active secukinumab treatment groups with:

- No load regimen of doses of 150 mg s.c. administered every 4 weeks
- Loading regimen at 150 mg s.c. administered at BSL, Weeks 1, 2 and 3, followed by a maintenance regimen of 150 mg s.c. every 4 weeks starting at Week 4.

- Loading regimen at 300 mg s.c. administered at BSL, Weeks 1, 2 and 3, followed by a maintenance regimen of 300 mg s.c. every 4 weeks starting at Week 4.

The loading regimen is supported by model-based analyses using data from psoriasis studies, predicting significantly improved PASI75 response rate after 12 weeks of treatment, compared to the response rates with monthly dosing. A loading regimen with four weekly doses of either 150 mg s.c. or 300 mg s.c. is expected to sustain rapid onset and greater magnitude of the effect of secukinumab on PASI75 and PASI90 in patients with PsA and psoriasis. The loading regimen with four weekly doses of either 150 mg s.c. or 300 mg s.c. is also expected to have a rapid and improved effect on the inhibition of structural damage. The approach for the no-load regimen has also been employed in this study to investigate the onset and sustainability of efficacy of secukinumab 150 mg s.c. administered every 4 weeks in patients with PsA. Assessment of joint and/or bone structure preservation is planned to be assessed using X-ray modality.

In summary, the maintenance regimens in this study aims at ensuring: a) optimal efficacy in PsA signs and symptoms, b) optimal efficacy in the treatment of skin disease in patients with concomitant psoriasis and c) optimal efficacy in inhibiting the progression of structural damage.

Formulation to be used

This study will use secukinumab liquid in PFSs. Secukinumab at 150 mg administered in PFSs has been substantiated in study CAIN457A2308 in the indication of plaque-type psoriasis and in study CAIN457F2312 in the indication of PsA. This study (CAIN457F2342) is the third study to test secukinumab in PFSs in the indication of PsA.

3.4 Rationale for choice of comparator

A placebo group is included in this study up to the Week 24. Due to the nature of the disease and the primary outcome measure used (ACR20 response), a placebo group is necessary to obtain reliable efficacy measurements for comparison between the active treatment groups and placebo in a controlled fashion. It is necessary to maintain placebo up to Week 24 to evaluate secukinumab treatment effect on radiographic evidence of structural inhibition at Week 24. The continuation of the placebo group up to Week 24 can be supported from an ethical standpoint. Firstly, treatment duration of the placebo group is kept to a minimum and the patients in placebo group will start receiving active treatment at the end of Week 16 or Week 24 (either secukinumab 150 mg s.c. or 300 mg s.c.) depending upon whether they are non-responders or responders, respectively at Week 16. Secondly, the regular assessments of disease activity ensures that subjects experiencing worsening of their disease in any of the treatment groups can exit the study upon their own wish or based on the advice of the investigator at any time. In addition, the inclusion of a placebo group is in accordance with health authority guidelines, including (FDA 1999/EMA 2006), and the parallel-group, placebo controlled design is in alignment with phase III trials of other biologics in this therapeutic domain as outlined in EMA guidelines (EMA 2006).

3.5 Purpose and timing of interim analyses/design adaptations

The primary endpoint analysis will be performed after all subjects have completed the visit associated with the key secondary radiographic endpoint (Week 24). Although the unblinding of the Novartis Clinical Team will occur after the Week 24 database lock, secukinumab regimen and original randomization to active treatment vs. placebo will continue to remain blinded to all investigators, site personnel, subjects, and monitors until the Week 52 database lock and analyses are completed.

Subsequent to the primary endpoint analysis, interim analyses are planned for regulatory submission and/or publication purposes after subjects have completed the Week 52 assessments. The X-Ray interpretation will be performed by an imaging service provider and readers will be blinded to the treatment as well as visit information. The final analysis will be conducted after all subjects have completed the study (Week F112). Additional analyses may be performed to support interactions with health authorities, as necessary.

3.6 Risks and benefits

Secukinumab has shown either preliminary or confirmed efficacy in several inflammatory diseases. The safety profile of secukinumab is primarily based on the aggregate safety data from 10 large completed phase II/III psoriasis trials. The evaluation of safety data from completed PsA trials did not show additional safety concerns.

Secukinumab was generally safe and well-tolerated. The most frequently reported adverse events (AE) are infections, especially upper respiratory tract with secukinumab relative to placebo. There was an increase in mucosal or cutaneous candidiasis with secukinumab compared to placebo, but the cases were generally mild or moderate in severity, non-serious, and responsive to standard treatment.

There was a small increase in mild neutropenia cases with secukinumab compared to placebo. Common Toxicity Criteria (CTC) AE grade 3 neutropenia (<1.0-0.5×10^9/L) was uncommonly observed with secukinumab, most were transient and reversible without a temporal relationship to serious infections.

Hypersensitivity reactions include urticarial and rare event of anaphylactic reaction to secukinumab were also observed in clinical studies.

Taking into account the individual risks as outlined above, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated to be similar or improved compared to the approved inflammatory cytokine-targeting therapies. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring and extensive guidance to the investigators, provided in the current version of the IB.

From the standpoint of the overall risk-benefit assessment, current trial with secukinumab is justified.

4 Population

The study population will be comprised of the subjects who have passed screening assessments and comply with eligibility criteria.

Subjects can be re-screened only once and no re-screening study related procedures should be performed prior to written re-consent by the subject. Mis-randomized subjects will not be re-screened.

This is an international study and it is expected that approximately 990 subjects will be randomized.

A screening failure rate of 20% and post-randomization dropout rate of 25% is anticipated in the first year. Enrollment will stop as soon as the target number and proportions of randomized subjects in the respective treatment group is reached.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Subject must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed.
2. Male or non-pregnant, non-lactating female subjects at least 18 years of age.
3. Diagnosis of PsA classified by CASPAR criteria (see Appendix 1) and with symptoms for at least 6 months with moderate to severe PsA who must have at BSL ≥3 tender joints out of 78 and ≥3 swollen joints out of 76 (dactylitis of a digit counts as one joint each).
4. Rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies negative at screening.
5. Diagnosis of active plaque psoriasis or nail changes consistent with psoriasis or a documented history of plaque psoriasis.
6. Subjects with PsA should have taken NSAIDs for at least 4 weeks prior to randomization with inadequate control of symptoms or at least one dose if stopped due to intolerance to NSAIDs.
7. Subjects who are regularly taking NSAIDs as part of their PsA therapy are required to be on a stable dose for at least 2 weeks before study randomization and should remain on a stable dose up to Week 24.
8. Subjects taking corticosteroids must be on a stable dose of ≤10 mg/day prednisone or equivalent for at least 2 weeks before randomization and should remain on a stable dose up to Week 24.
9. Subjects taking MTX (≤ 25 mg/week) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization and should remain on a stable dose up to Week 52.
10. Subjects on MTX must be on folic acid supplementation at randomization.
11. Subjects who are on a DMARD other than MTX must discontinue the DMARD 4 weeks prior to randomization visit except for leflunomide, which has to be discontinued for 8 weeks prior to randomization unless a cholestyramine wash-out has been performed.
12. Subjects who have been on a TNFα inhibitor must have experienced an inadequate response to previous or current treatment with a TNFα inhibitor given at an approved dose for at least 3 months or have stopped treatment due to safety/tolerability problems after at least one administration of a TNFα inhibitor.

13. Subjects who have previously been treated with TNFα inhibitors (investigational or approved) will be allowed entry into study after appropriate wash-out period prior to randomization:
    a. 4 weeks for Enbrel® (etanercept) – with a terminal half-life of 102 ± 30 hours (s.c. route).
    b. 8 weeks or longer for Remicade® (infliximab) – with a terminal half-life of 8.0-9.5 days (i.v. infusion).
    c. 10 weeks or longer for Humira® (adalimumab) – with a terminal half-life of 10-20 days (average 2 weeks) (s.c. route).
    d. 10 weeks or longer for Simponi® (golimumab) – with a terminal half-life of 11-14 days.
    e. 10 weeks or longer for Cimzia® (certolizumab) – with a terminal half-life of approx. 14 days.

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Chest X-ray or chest MRI with evidence of ongoing infectious or malignant process obtained within 3 months prior to screening and evaluated by a qualified physician.
2. Subjects taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine).
3. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor.
4. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer.
5. Ongoing use of prohibited psoriasis treatments / medications (e.g., topical corticosteroids, UV therapy) at randomization. The following wash out periods need to be observed:
    a. Oral or topical retinoids: 4 weeks.
    b. Photochemotherapy (e.g. PUVA): 4 weeks.
    c. Phototherapy (UVA or UVB): 2 weeks.
    d. Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency): 2 weeks.
6. History of hypersensitivity to the study drug or its excipients or to drugs of similar classes.
7. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization.
8. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization.
9. Subjects who have previously been treated with more than 3 different TNFα inhibitors (investigational or approved).
10. Subjects who have ever received biologic immunomodulating agents except for those targeting TNFα (investigational or approved).

11. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19).
12. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment and minimum 16 weeks or longer if local label requires it (e.g. 20 weeks in EU) after the last dose. Effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
    - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.

    NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
14. Active ongoing inflammatory diseases other than PsA that might confound the evaluation of the benefit of secukinumab therapy.
15. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in an immunomodulatory therapy.
16. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure [New York Heart Association status of class III or IV], and uncontrolled diabetes.

17. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests (LFT) such as aspartate aminotransferase/serum glutamic oxaloacetic transaminase (AST/SGOT), alanine aminotransferase/ serum glutamic pyruvic transaminase (ALT/SGPT), alkaline phosphatase, or serum bilirubin. The investigator should be guided by the following criteria:
    a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrollment/randomization, to rule out lab error.
    b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dL (27 µmol/L).
18. History of renal trauma, glomerulonephritis, or subjects with one kidney only, or a serum creatinine level exceeding 1.5 mg/dL (132.6 µmol/L).
19. Screening total white blood cell (WBC) count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or hemoglobin <8.5 g/dL (85 g/L).
20. Active systemic infections during the last two weeks (exception: common cold) prior to randomization.
21. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive PPD skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule Table 6-1. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis. If presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.
22. Known infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C at screening or randomization.
23. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed).
24. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the subject unsuitable for the trial.
25. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins).
26. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol.
27. Donation or loss of 400 mL or more of blood within 8 weeks before randomization.
28. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization.

29. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

Novartis will supply the following:

- Investigational treatment
  Secukinumab 150 mg provided in 1 ml PFS
- Reference treatment
  Secukinumab placebo provided in a 1 ml PFS.

Subjects will be instructed by site staff on how to self-administer the s.c. injection using the PFS, based on the Instructions for Use (IFU). The investigational drug will be administered by the subject into the appropriate injection site of the body under the supervision of the site staff. All injections through Week 52 will be performed at the study site. After Week 52, the subject may elect to self-administer the study treatment at home when they are not visiting the site for any other trial related procedures.

The PFSs are packed in a double blinded fashion and do not need to be prepared. The study treatments will be labeled as follows:

- Double blind secukinumab and placebo PFS will be labeled AIN457 150 mg/1 ml/Placebo for dosing till Week 52.
- Open label secukinumab PFS will be labeled AIN457 150mg/1ml.

For detailed instructions on storage of the investigational treatments, please refer to Section 5.5.3.

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

5.2 Treatment arms

Subjects will be randomized to one of the following five treatment arms in a 4:4:4:3:3 ratio, with 220 subjects in each of the first three treatment arms and 165 in each of the fourth and fifth treatment arm as depicted below:

- Arm 1: secukinumab 150 mg s.c. without loading regimen:
  secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) administered at BSL, placebo (2 x 1.0 mL PFS) administered on Weeks 1, 2 and 3, followed by secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) dosing every four weeks starting at Week 4.
- Arm 2: secukinumab 150 mg s.c. with loading dose regimen:

secukinumab 150 mg (1.0 mL PFS of 150 mg dose) and placebo (1.0 mL PFS) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4.

- Arm 3: secukinumab 300 mg s.c. with loading dose regimen:
  secukinumab 300 mg (2 x 1.0 mL PFS of 150 mg dose) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4.
- Arm 4: placebo s.c. followed by secukinumab 150mg at Week 16 or 24:
  placebo (2 x 1.0 mL PFS) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4, and switch to secukinumab 150 mg (1.0 mL PFS of 150 mg dose) at Week 16 or 24. Subjects who don't respond to the joint criteria at Week 16 will be escaped (i.e. receive their pre-assigned secukinumab treatment starting at Week 16). Otherwise, they will continue to receive placebo until Week 24 at which time they will switch to their pre-assigned secukinumab treatment.
- Arm 5: placebo s.c. followed by secukinumab 300 mg at Week 16 or 24:
  placebo (2 x 1.0 mL PFS) administered at BSL, Weeks 1, 2 and 3, followed by dosing every four weeks starting at Week 4, and switch to secukinumab 300 mg (2 x 1.0 mL PFS of 150 mg dose) at Week 16 or 24. Subjects who don't respond to the joint criteria at Week 16 will be escaped (i.e. receive their pre-assigned secukinumab treatment starting at Week 16). Otherwise, they will continue to receive placebo until Week 24 at which time they will switch to their pre-assigned secukinumab treatment.

Note that the treatment arms 4 and 5 together form placebo treatment group (Group 4) as described in Figure 3-1.

Although the number of subjects on the placebo group is higher than any of the individual secukinumab groups, when considering the ratio of secukinumab (all three groups) vs. placebo, the ratio is 2:1. This is justifiable from an ethical standpoint and the statistical justification is provided in Section 3.1.

Subjects will receive treatment at BSL, Week 1, 2 and 3, followed by treatment every 4 weeks starting at Week 4. Subjects will self-administer all secukinumab and placebo doses through Week 104 (with last dose given at Week 100).

At Week 16, subjects who have been randomized to secukinumab groups at BSL (Groups 1-3) will be classified as either responders (≥20% improvement from BSL in both TJC and SJC) or non-responders (<20% improvement from BSL TJC or SJC), however they will continue on the same treatment irrespective of their response status. However the non-responders, defined as subjects with <20% improvement from BSL in TJC or SJC, and originally randomized to placebo at BSL (Group 4) will receive either secukinumab 150 mg (one injection each of secukinumab 1 mL/150 mg and 1 mL placebo for 150 mg) or secukinumab 300 mg (two injections of secukinumab 1 mL/150 mg) in a double-blinded fashion (as dictated by treatment sequence assigned to these subjects at BSL).

At Week 24, the remaining subjects originally randomized to placebo (Group 4) and who continued receiving placebo s.c. injection after Week 16 will receive secukinumab 150 mg (one injection each of secukinumab 1 mL/150 mg and 1 mL placebo for 150 mg) or secukinumab 300 mg (2 injections of secukinumab 1 mL/150 mg) in a blinded fashion (as dictated by

treatment sequence assigned to these subjects at BSL). Therefore, after Week 24, all subjects in every treatment arm will receive 2 PFS injections (either 2 x 150 mg/mL for 300 mg or 1 x 150 mg/mL of secukinumab + 1 mL placebo for 150 mg) in a blinded fashion until open-label treatment is started.

Subjects will self-administer all secukinumab and placebo doses at the study site through Week 52.

Beginning at Week 52, for subjects whose signs and symptoms are not fully controlled, and who the investigator believes may improve further with an increase in dose, may have the secukinumab dose increased to 300mg s.c. every 4 weeks. This will be performed in a blinded manner until after the Week 52 interim analysis database lock is performed.

After the Week 52 database lock and analyses have been completed, site personnel and subjects will be unblinded to the original randomized treatment (sequence) assignment. In addition, study treatment will be given open-label to eliminate the need for placebo injections in subjects on secukinumab 150 mg, which were previously given to maintain the blind. **After Week 52**, subjects may elect to administer the PFS at home when they are not visiting the site for any other trial related procedures. Typically the trial related safety and efficacy procedures will be conducted every 12-16 weeks after Week 52. Thus between two site visits after Week 52 (Table 6-2), subjects may self-administer the treatment via PFS at home, which also permits less frequent study site visits.

5.3 Treatment assignment, randomization

At BSL, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the five treatment arms as described in Section 5.2. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to the site staff.

At Week 16, the investigator must contact the IRT in order to record the subject's responder status (responder/non-responder based on ≥ 20% improvement in both swollen and tender joint counts) after the subject has been assessed. The IRT will not generate the medication number of PFSs to be administered at Week 16, if the subject's responder status is missing. After receiving the responder status IRT will assign the medication number of the PFS to be administered. IRT will only communicate to the caller the medication numbers.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

Subjects will be stratified at randomization on the basis of previous anti-TNF therapy as TNF-naïve or TNF-IR. Based on enrollment target, 70% of randomized subjects will be TNF-naïve and 30% TNF-IR to ensure a representative subject population for the assessment of efficacy and safety.

The randomization scheme for subjects will be reviewed and approved by a member of the Integrated Quantitative Sciences (IQS) Randomization Group.

5.4 Treatment blinding

This is a double-blind randomized treatment trial. Subjects, investigators, site personnel, and persons performing the assessments will remain blinded to treatment assignment from the time of randomization until the Week 52 database lock and analyses are completed, using the following methods:

1. Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study with the exception of the bioanalyst
2. The identity of the treatments will be concealed up to the Week 52 database lock and analyses are completed by the use of study treatments in the form of PFS for s.c. injection, filled with secukinumab or placebo that are identical in appearance.

Unblinding of treatment dose or original randomized treatment assignment before the Week 52 database lock and analyses are completed will only occur in the case of subject emergencies (see Section 5.5.12).

The hsCRP results from samples collected during the treatment period will be revealed only after the Week 52 database lock and analyses are completed.

The X-Ray interpretations performed by central Imaging Contract Research Organization (CRO) personnel will not be disclosed to investigators, site personnel, subjects and monitors during the trial.

The primary efficacy analysis will be performed when the database is locked (after all subjects have completed Week 24 assessments). Summary results may be shared internally and externally; however, individual unblinded subject data will not be disclosed. Data analysts will not remain blinded after the Week 24 database lock. A final database lock will occur when all subjects have completed the study.

5.5 Treating the subject

5.5.1 Subject numbering

Each subject is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a subject, the Subject Number will not be reused.

Upon signing the informed consent form, the subject is assigned the next sequential number by the investigator. The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. The site should select the case report form (CRF) book with a matching Subject Number from the electronic data capture (EDC) system to enter data.

If the subject fails to be treated for any reason, the IRT must be notified within 2 days that the subject was not treated. The reason for not being treated will be entered on the Screening Epoch Study Disposition CRF.

Subjects may be re-screened once and will receive a new Subject Number after they have been re-consented. Subjects who are mis-randomized cannot be re-screened.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with investigational treatment in packaging of identical appearance.

The investigational treatment packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to placebo or active treatment. Investigator staff will identify the investigational treatment package(s) to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.3 Handling of study treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Pharma Organization (CPO) Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the subject except for the medication number.

The PFS (150 mg active/placebo) sealed in their outer box must be stored in a access controlled/locked refrigerator between 2°C and 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. They must be carefully controlled in accordance with regulations governing investigational medicinal products and local regulations.

If the subject will be self-administering treatment at home (after Week 52), the investigator should ensure the subject can store the medication according to these conditions before allowing the subject to self-administer at home.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a Drug Accountability Log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused investigational treatment and packaging at the next site visit, at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all partly used and unused investigational treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis as instructed.

Destruction of the unused drug should be done according to local requirements and after approval by the Novartis Clinical Team.

5.5.4 Instructions for prescribing and taking study treatment

Study treatment (150 mg secukinumab and placebo) will be administered by s.c. PFSs throughout the study. Administration of study treatment will occur at the study site through Week 52. Administration of study treatment must occur after the study assessments for the visit have been completed. After Week 52, subjects will be allowed to self-administer the study treatment at home during the optional visits in which there are no scheduled assessments at the site (see Home Administration in Table 6-2 below).

The PFS with the ready-to-use study treatment solution will be provided by the site staff to the subject. Detailed instructions on the self-administration of the study treatment will be described in the Instructions For Use (IFU) and provided to each subject.

At the BSL visit, subjects will be instructed by the site staff, utilizing the IFU, on how to self-inject using a PFS. Subjects will be asked to raise questions, if they have any, and then to proceed with self-injection. At the Week 1 visit, subjects will be asked to refer to the IFU and to proceed directly with self-injection of the study drug (i.e., no prior retraining) for the remainder of the trial. However, if the subject is not comfortable self-injecting the study treatment, then the site staff may administer it for the subject.

All study treatment kits assigned to the subject during the study will be recorded in the IRT.

The first study treatment administration will occur at the BSL/randomization visit only after eligibility criteria have been confirmed, all study scheduled BSL assessments have been performed and the scheduled blood samples have been drawn.

At each subsequent visit, all study assessments, including the completion of Patient Reported Outcomes (PROs), (as applicable per Table 6-1 and Table 6-2), should be completed prior to the self-injection of study treatment.

[redacted]

The investigator should promote compliance by instructing the subject to attend the study visits as scheduled and by stating that compliance is necessary for the subject's safety and the validity

of the study. The subject should be instructed to contact the investigator if he/she is unable for any reason to attend a study visit as scheduled or if he/she is unable for any reason to take the study treatment as prescribed.

5.5.4.1 Subcutaneous administration with PFSs

Secukinumab solution for subcutaneous injection (150 mg in 1.0 mL active/placebo) will be provided in PFSs.

The study treatment solution **must** be injected into **non-affected** areas of the skin.

Subjects will be instructed by the site staff on how to self-inject study treatment using a PFS, following the IFU. The injections will be self-administered into the appropriate site of the body (thighs, arms, abdomen), and each injection should be given at a different injection site to reduce the risk of reaction. Each new injection should be given at least one inch from the previously used site. If subject chooses the abdomen, a 2 inch area around the navel should be avoided. Investigational drug should not be injected into areas where the skin is tender, bruised, red, or hard, or where subject has scars or stretch marks.

Single PFSs will be packaged in individual boxes. The boxes containing the PFSs with study treatment solution should be kept at 2 to 8°C (36°F and 46°F) (Do Not Freeze) and protected from light. Prior to administration the boxes containing the PFSs with study treatment solution should be allowed to come to room temperature **unopened** for 15-30 minutes prior to injection. Used PFSs should be disposed immediately after use in a sharps container OR according to the regulatory needs of the respective countries.

Any PFS for which a defect or malfunction is noticed prior to or during the injection at any of the study visits, must be kept at the site until guidance is received from Novartis on whether it should be returned to Novartis for investigation or discarded. Devices identified as defective should be stored according to local guidelines, until specific instruction is discussed with Novartis personnel. Additionally, from BSL onwards, any noticed defect, malfunction, problem during the injections or product complaints with the PFS should be recorded in the source document and the Use of Device electronic case report form (eCRF). Sites should detail the issue, the date, the kit number and the visit number. Site will be asked to record based on their judgment whether the observed issue was primarily related to the device or to the user. Device malfunctions should also be immediately reported to Novartis personnel as a necessary replacement kit may need to be provided.

5.5.4.2 Home administration

Up to Week 52, all doses of study treatment will be self-administered by the subject at the study site, after the study assessments for the visit have been completed. After Week 52 the subjects will be allowed to self-administer the study treatment at home during the optional visits period when there are no scheduled site assessments. Optional site visits are included in the assessment table (Table 6-2) and during these visits trial related procedures are to be conducted. Subjects will be allowed to self-administer the study treatment via PFS at home or to visit the site during the optional visits to self-administer study treatment under the supervision of the site staff. If the subject opts for home administration of study treatment and is unable or unwilling to self-administer the treatment via PFS, a care-giver may administer the study treatment during

Treatment period 3 only. Caregivers should be trained on the IFU prior to administering the study treatment to the subject. It should be recorded on the Dose Administration Record eCRF(s) whether the subject self-administered the study treatment at home or at the site and if a caregiver administered the treatment**.**

Prior to self-administration at home, subjects should contact the investigator / site staff in case they are experiencing any AE/SAEs, or have any concerns.

All dates and times of self-administrations by the subject during the study must be recorded on the Dosage Administration Record eCRF. Immediately before dispensing the package to the subject, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Study treatment dose adjustments are not permitted. Study treatment interruption should be avoided with the following exceptions:

Study treatment interruption is only permitted if, in the opinion of the investigator, a subject is deemed to be placed at a significant safety risk unless dosing is temporarily interrupted. In such cases study treatment should be interrupted only during the time that this risk is present and ongoing. Study treatment can be restarted at the next scheduled visit after resolution of the safety risk.

The effect of secukinumab on live vaccines is unknown; therefore live vaccines should not be administered during participation in the study. In case a live vaccine has been administered due to a medical urgency, study treatment should be interrupted for 12 weeks.

Any study treatment interruption must be recorded on the corresponding eCRF page.

5.5.6 Rescue medication

Rescue medication is defined as any new therapeutic intervention or a significant change to ongoing therapy made because a subject is experiencing either no benefit from participation in the trial or worsening / exacerbation of their disease.

Rescue medication must not be used before completion of Week 24 assessments (see Section 3.1). Please see Section 5.5.7 and Section 5.5.8 for details. Although no subject will be restricted from receiving necessary rescue medications for lack of benefit or worsening of disease, if rescue with prohibited treatments (as described in Section 5.5.8) occurs prior to completion of Week 24 assessments, subjects will be discontinued from the study and enter into the follow-up period after an End of Study visit. Efficacy will be assessed in detail at every study visit, and subjects who are deemed not to be benefiting from the study treatment based upon safety and efficacy assessments by the investigator or for any reason on their own accord will be free to discontinue participation in the study at any time.

Changes in NSAIDs concomitant therapy is permitted after Week 24 assessments as per investigator's clinical judgment.

After Week 52, the dose and regimen of other concomitant medications may be adjusted slowly at the investigator's discretion and recorded appropriately on the CRF page.

5.5.7 Concomitant treatment

The investigator should instruct the subject to notify the study site about any new medications (including over-the-counter drugs, calcium and vitamins) administered after the subject was enrolled into the study. All medications (other than study treatment), procedures and significant non-drug therapies (including physical therapy and blood transfusions) must be recorded on the Prior and Concomitant medications or Procedures and Significant Non Drug Therapy eCRF. The reason, name of the drug, procedure or non-drug therapy should be listed.

Guidelines for the use of specific medications are provided below:

Methotrexate

Subjects taking MTX (up to 25 mg/week) must be on a stable dose for at least 4 weeks before randomization and maintained stable until Week 52.

Folic acid

Subjects on MTX must be taking folic acid supplementation before randomization and during the trial to minimize the likelihood of MTX associated toxicity.

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment, a drug wash-out of 8 weeks has to be performed. However, another wash-out procedure might be considered. Cholestyramine could be given orally to wash-out the drug at a dose of 8 g t.i.d. Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40% in 24 hours and by 49% to 65% in 48 hours in three healthy volunteers. The administration of cholestyramine is recommended in subjects who require a drug elimination procedure. If a subject receives 8 g t.i.d. for 11 days he/she could be safely randomized 4 weeks after the beginning of the 11 days treatment period.

Systemic corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomization. The subject should remain on a stable dose until Week 24.

Corticosteroid dose reductions below 10 mg prednisone equivalent are permitted after Week 24, although the corticosteroid dose should not be reduced more than 1 mg prednisone equivalent every 4 weeks.

After Week 52, the dose and regimen of systemic corticosteroids may be modified as per investigator's judgment and subject need.

Any change in the dose of systemic corticosteroids during the trial must be recorded on the corresponding eCRF page.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomization and up to Week 24. After Week 24, no more than 1 joint per 24-week period may be injected. No single injection should exceed 40 mg of triamcinolone (or equivalent) and the total dose of intra-articular corticosteroid may not exceed 80 mg of triamcinolone (or equivalent) during any

52-week period. Injection of intra-articular steroids is not permitted within 8 weeks prior to Weeks 52 and 104.

Non-steroidal anti-inflammatory drugs (NSAIDs) (including COX-1 or COX-2 inhibitors), low strength opioids and acetaminophen/paracetamol

Subjects on regular use of NSAIDs, low strength opioids, or paracetamol/acetaminophen as required (PRN) should be on stable dose for at least 2 weeks before randomization to allow inclusion. They should remain on a stable dose in the study up to Week 24, however, they have to refrain from any intake during at least 24 hours before a visit with disease activity assessment.

After Week 24 assessments are completed, a change in the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment regimen is permitted.

Any change of the NSAIDs, low strength opioids, or paracetamol/acetaminophen treatment during the trial should be recorded on the corresponding eCRF page.

5.5.8 Prohibited Treatment

Use of the treatments displayed in Table 5-1 is NOT allowed after the start of the washout period unless specified otherwise below.

Live vaccines should not be given until 12 weeks after last study treatment administration.

Table 5-1 Prohibited treatments

Prohibited treatments	Washout period (before randomization)
Biological immunomodulating agents > 3 different TNFα	Never
Etanercept*	4 weeks
Infliximab*	8 weeks
Adalimumab, golimumab, certolizumab*	10 weeks
DMARDs (except MTX)	4 weeks
Apremilast	4 weeks
Leflunomide	8 weeks
Leflunomide with Cholestyramine washout	4 weeks
Unstable dose of NSAIDs (including COX1 or COX2 inhibitors)	2 weeks
(until Week 52)	
Analgesics other than NSAIDs, paracetamol/acetaminophen and low strength opioids PRN	2 weeks
Systemic corticosteroids > 10 mg prednisone equivalent** (until Week 52)	2 weeks
Unstable dose of systemic corticosteroids <= 10 mg prednisone equivalent (until Week 24)	2 weeks
Intra-articular injections (until Week 24)	4 weeks
Intramuscular or intravenous corticosteroid treatment	4 weeks
Any investigational treatment or participation in any interventional trial	4 weeks or 5 half-lives (whichever is longer)

Prohibited treatments	Washout period (before randomization)
Live vaccinations	6 weeks
Oral or topical retinoids	4 weeks
Photochemotherapy (e.g. PUVA)	4 weeks
Phototherapy (UVA or UVB)	2 weeks
Topical skin treatments (except in face, eyes, scalp and genital area during screening, only corticosteroids with mild to moderate potency)	2 weeks

* These agents fall under the category of biologic immunomodulators and are prohibited medications. Administration of these agents requires study discontinuation (see Section 5.5.9).
** See details about corticosteroid management in Section 5.5.7

5.5.9 Discontinuation of study treatment

Subjects may voluntarily discontinue from the study for any reason at any time. They may be considered discontinued if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature discontinuation occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature discontinuation from the study and record this information on the appropriate Study Phase Completion eCRF.

Study treatment must be discontinued if the investigator determines that continuation of study treatment would result in a significant safety risk for a subject.

The following circumstances **require** study treatment discontinuation:

- Withdrawal of informed consent
- Subject's request to terminate treatment
- Emergence of the following AEs:
  - Any severe or serious AE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable co-medication
  - Onset of lymphoproliferative disease or any malignancy except for treated basal cell carcinoma, treated actinic keratoses, treated in situ carcinoma of the cervix or non-invasive malignant colon polyps which are being or have been removed
  - Life-threatening infection
  - Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study (A general guidance on clinically notable laboratory values is provided in Appendix 8).
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any protocol deviation that results in a significant risk to the subject's safety.

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if there is a lack of improvement or worsening

of their symptoms, or if on balance, he/she thinks that continuation would be detrimental to the subject's well-being. The investigator should discontinue from study treatment subjects who have <20% improvement from BSL in either TJC or SJC at both Week 40 and Week 44.

For subjects who discontinue study treatment, a Dosage Administration Record eCRF should be completed, giving the date and primary reason for stopping study treatment.

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

For subjects who prematurely discontinue or withdraw during a specific treatment period, the investigator should ensure that the subject completes an End of Study visit (corresponds to the last visit for the current period of treatment, e.g. Weeks 24, 52 and 104) 4 weeks after last study treatment and also return for the final Follow-up visit at Week F112 (12 weeks after last study treatment, see Table 6-1 and Table 6-2). Even if the subject is not willing to come back for all assessments, every effort should be made to collect the scheduled X-ray assessments. The final visit should be performed before any new treatment is initiated.

5.5.10 Withdrawal of consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs when a subject does not want to participate in the study anymore, that is, the subject does not want any further visits, assessments, or study related contacts, and does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information in the Withdrawal of Consent eCRF. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

5.5.11 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by contacting the subject, family or family physician as agreed in the informed consent and by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled End of Study visit would have occurred.

5.5.12 Emergency breaking of assigned treatment code

Emergency treatment code breaks should only be undertaken when it is essential to treat the subject safely and efficaciously. Most often, study discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an

emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Global Trial Lead (GTL) or designee that the code has been broken.

It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. The investigator will inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable. The investigator will provide protocol number CAIN457F2342, study drug name if available, subject number, and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case an emergency unblinding is required at a time when the investigator and backup are unavailable.

Study drug must be discontinued after emergency unblinding.

5.5.13 Study completion and post-study treatment

A subject will be considered to have completed the study if he/she received a total of 104 weeks of study treatment and upon completion of the scheduled study assessments and procedures up to and including Visit F112.

Information on the subject's completion or discontinuation of the study and the reason for discontinuation of the study will be recorded on the appropriate Study Phase Completion eCRF page.

In any case, the investigator or site staff must contact the IRT as soon as possible to record the subject's study completion (Visit F112) and/or discontinuation.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care. This care may include initiating another treatment outside of the study as deemed appropriate by the investigator. This treatment may be any non-biologic DMARD. In case of a biologic treatment, a waiting period of 3 months before initiating the treatment is recommended.

5.5.14 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

6 Visit schedule and assessments

Table 6-1 and Table 6-2 list all study assessments and indicates with an "X" when they are performed.

During the period of the study from SCR to Week 52, the assessments must be performed as indicated in Table 6-1. For the post-Week 52 period of the study and the final follow-up visit, the assessments are outlined in Table 6-2 (Week 56 to Week 104 and Follow-up Week F112).

Subjects should be seen for all visits on the designated day, or as closely as possible to the original planned visit schedule.

- For visits scheduled through Week 4, the study treatment should not be administered less than 7 days from the previous administration.
- For visits scheduled after Week 4, the study treatment should not be administered less than 14 days from the previous administration.

Subjects who prematurely discontinue during a specific treatment period should return for the final visit within that treatment period (4 weeks after the last study treatment), as well as return for the follow-up visit (Week F112), 12 weeks after the last study treatment.

If subjects refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the reason. Documentation of attempts to contact the subject should be recorded in the source documentation.

Screening will be flexible in duration based on the time required to wash out prior anti-rheumatic medications and have duration of 4-10 weeks, during which time the subject will sign the ICF, be evaluated for eligibility and allowed sufficient time for potential medication washout (see Table 5-1, in addition to all other assessments indicated in Table 6-1).

Screening will consist of two consecutive visits. During the first SCR visit, initial assessments will be performed as outlined in Table 6-1. At that visit the duration of the washout period will be determined. The second SCR visit will be performed as follows:

- If the washout period is ≤ 4 weeks the investigator should proceed directly to SCR visit 2 on the same day and complete all assessments in the next 4 weeks prior to randomization.
- If the washout period is more than 4 weeks, the subject will be instructed to initiate necessary washout regimen and return for SCR visit 2 at 4 weeks prior to randomization.

The rationale is that in all cases SCR visit 2 must occur within the 4 weeks prior to randomization.

If subjects do not have a chest X-ray obtained within 3 months preceding the SCR visit, a chest X-ray should be performed. In order to minimize unnecessary exposure to radiation, the chest X-ray should only be performed after confirming that the subject meets all inclusion/exclusion criteria. In some sites selected by Novartis, the X-ray assessment may be replaced by MRI assessment.

All subjects evaluated at SCR visits 1 and 2 for eligibility should not be screen failed on the basis of a medication requiring washout, unless the subject will be unable to complete the washout in the appropriate time frame before randomization.

Subjects who prematurely withdraw from the study will not be replaced.

Table 6-1 Assessment schedule – Part 1: Screening to Week 52

	Screening[1]		Treatment Period 1										Treatment Period 2						
Week	-10 to -4	≤ -4 to BSL	BSL	1	2	3	4	8	12	16	20	24* TD/ PSW	28	32	36	40	44	48	52* TD/ PSW
Informed consent & optional PG informed consent	X																		
Inclusion/Exclusion criteria	X	X	X																
Hepatitis B, C or HIV serology (only in countries where it is required)[2]	X																		
Relevant medical history/ current medical condition	X																		
Washout evaluation/instruction	X																		
Smoking history			X																
Cardiovascular medical history			X																
Demography	X																		
Psoriasis/psoriatic arthritis medical history and previous therapies	X																		
PsA CASPAR Criteria		X																	
Physical Exam		S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S	S
Height		X																	
Weight		X	X							X		X							X
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPD skin test[3] or QuantiFERON TB Gold test		X																	
Chest X-ray / MRI[4]		S																	

	Screening[1]		Treatment Period 1										Treatment Period 2						
Week	-10 to -4	≤ -4 to BSL	BSL	1	2	3	4	8	12	16	20	24* TD/ PSW	28	32	36	40	44	48	52* TD/ PSW
ECG			X							X									X
Randomization via IRT			X							X[5]		X[6]							
Administration of s.c. study treatment via PFS at study site			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/Concomitant medication/non-drug therapy	X	Update as necessary																	
Adverse Events/SAEs[7] (incl. injection site reaction & occurrence of infections)	X	Update as necessary																	
Hematology, blood chemistry, urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X		X			X
Serum pregnancy test		X																	
Urine pregnancy test[8]			X				X		X	X		X		X		X			X
ANA			X							X		X							X
Anti-dsDNA			X							X		X							X
[redacted]																			
Anti-CCP	X																		
Rheumatoid factor (RF)	X																		
[redacted]																			
High sensitivity C-Reactive protein (hsCRP)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Erythrocyte Sedimentation Rate (ESR)[8]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
X-ray (hands/wrists + feet)			X							X[9]		X[10]							X

	Screening[1]		Treatment Period 1										Treatment Period 2						
Week	-10 to -4	≤ -4 to BSL	BSL	1	2	3	4	8	12	16	20	24* TD/ PSW	28	32	36	40	44	48	52* TD/ PSW
Tender and swollen joint counts (TJC78, SJC76)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's assessment of PsA pain (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]																			
Physician's global assessment of disease activity (VAS)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Health Assessment Questionnaire (HAQ-DI©)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted] Dactylitis [redacted]			X	X	X	X	X	X	X	X		X		X		X			X
[redacted] Enthesitis [redacted]			X	X	X	X	X	X	X	X		X		X		X			X
[redacted]																			
PASI			X	X	X	X	X	X	X	X		X		X		X			X
[redacted]																			

	Screening[1]		Treatment Period 1										Treatment Period 2						
Week	-10 to -4	≤ -4 to BSL	BSL	1	2	3	4	8	12	16	20	24* TD/ PSW	28	32	36	40	44	48	52* TD/ PSW
[redacted]																			
Lipids[11]			X					X		X		X							X
Cardiovascular panel			X							X		X							X
[redacted]																			
Treatment period 1 completion form												X							
Treatment period 2 completion form																			X

[1] If subject's washout period is ≤ 4 weeks, the two screening visits can be performed on the same day.

[2] Hepatitis B and/or hepatitis C and/or HIV serology testing performed during screening period only if required as per local medical practice or local regulators prior to initiation of therapy. These assessments will be documented in source records only and will not be entered into the eCRFs.

[3] The PPD skin test can be performed at any time during the screening period but it has to be read within 72 hrs and before randomization.

[4] If subjects do not have a chest X-ray available within 3 months of screening, an X-ray should be performed after it is certain the subject meets inclusion/exclusion criteria in order to minimize unnecessary exposure to X-ray radiation. In some sites selected by Novartis, the X-ray assessment may be replaced by chest MRI assessment.

[5] non-responder subjects (with <20% improvement from BSL in TJC or SJC) in the placebo group (Group 4) will receive either secukinumab 150 mg or 300 mg s.c., as dictated by treatment assigned to these subjects at BSL.

[6] Subjects originally randomized to placebo group and who continue to receive placebo till Week 24 will receive either secukinumab 150 mg or 300 mg s.c., as dictated by treatment assigned to these subjects at BSL.

[7] AEs /SAEs occurring after the subject has provided informed consent must be reported.

[8] Kits will be provided by central lab and test is to be performed locally.

[9] X-rays are only taken for subjects who are non-responders at Week 16 (< 20% improvement from BSL in TJC or SJC).

[10] X-rays are taken for all subjects, both responders and non-responders at Week 16 (≥ 20% reduction from BSL in both TJC and SJC).

[11] Sample must be obtained fasting.

[redacted]

TD = study treatment discontinuation
PSW = Premature subject withdrawal
X = assessment to be recorded in clinical data base
S = assessment to be recorded on source documentation

* Subjects who prematurely discontinue during Treatment Period 1 should return for assessments associated with Week 24 visit (4 weeks after the last study treatment in Treatment Period 1) and the follow-up visit (Week F112) 12 weeks after the last study treatment. Subjects who prematurely discontinue during Treatment Period 2 should return and complete assessments associated with Week 52 visit (4 weeks after the last study treatment in Treatment Period 2) and the follow-up visit (Week F112) 12 weeks after the last study treatment.

Table 6-2 Assessment schedule - Part 2: Week 56 to Week 104 and Follow-up visit F112

	Treatment period 3													Follow -up
Week	56	60	64	68	72	76	80	84	88	92	96	100	104* TD/PSW	F112* TD/PSW
Optional site visit[1]	X		X		X		X		X		X			
Administration of s.c. study treatment via PFS	X	X	X	X	X	X	X	X	X	X	X	X		
Physical Exam		S		S		S		S		S		S	S	S
Weight						X							X	X
Vital signs		X		X		X		X		X		X	X	X
ECG						X							X	
Hematology, blood chemistry, urinalysis		X		X		X		X		X			X	
Urine pregnancy test[2]		X		X		X		X		X			X	
Concomitant medication/non- drug therapy	Update as necessary													
AE/SAE (including injection site reaction, occurrence of infection)	Update as necessary													
ANA													X	
Anti-dsDNA													X	
[redacted]														
High sensitivity C-Reactive protein (hsCRP)		X		X		X		X		X			X	X
Erythrocyte Sedimentation Rate (ESR)[2]		X		X		X		X		X			X	X
X-ray (hands/wrists + feet)													X[3]	
Tender and swollen joint counts (TJC78, SJC76)		X		X		X		X		X			X	
Patient's assessment of PsA pain (VAS)		X		X		X		X		X			X	
Patient's global assessment of disease activity (VAS)		X		X		X		X		X			X	
[redacted]														
Physician's global assessment of disease activity (VAS)		X		X		X		X		X			X	

	Treatment period 3													Follow -up
Week	56	60	64	68	72	76	80	84	88	92	96	100	104* TD/PSW	F112* TD/PSW
Health Assessment Questionnaire (HAQ-DI©)		X		X		X		X		X			X	
[redacted] Dactylitis [redacted]		X		X		X		X		X			X	
[redacted] Enthesitis [redacted]		X		X		X		X		X			X	
[redacted]														
PASI		X		X		X		X		X			X	
[redacted]														
Lipids[4]						X							X	
Cardiovascular panel													X	
[redacted]														
Treatment period 3 completion form													X	
Follow-up period completion form														X

[1] Apart from the visits listed as optional, the rest of the visits are mandatory, considering the required assessments on that visit

[2] Kits will be provided by central lab and test is to be performed locally.

[3] Subjects who discontinue will have X-rays taken only if more than 60 days have elapsed since their last X-rays.

[4] Sample must be obtained fasting.

TD = study treatment discontinuation
PSW = Premature subject withdrawal
X = assessment to be recorded on clinical data base
S = assessment to be recorded on source documentation

*Subjects who prematurely discontinue during Treatment Period 3 should return for assessments associated with the Week 104 visit (4 weeks after the last study treatment) and the follow-up visit (Week F112) 12 weeks after the last study treatment.

6.1 Information to be collected on screening failure

Subject may discontinue from the study prior to randomization. These subjects are considered screening failures.

If a subject discontinues before entering the double-blind treatment period at BSL, IRT must be notified within 2 days and the reason for not being randomized will be entered on the SCR Phase Disposition eCRF page. In addition, only the following eCRFs should be completed: Demography eCRF, Informed Consent eCRF, Inclusion/Exclusion eCRF, and the Adverse event (AE) eCRF should be completed for any Serious Adverse Events (SAEs) that occurred during the SCR period.

Adverse events that are not serious will be followed by the investigator and collected only in the source data.

All subjects who have signed informed consent and are randomized into the Treatment Period 1 of the study will have all AEs **occurring after informed consent is signed** recorded on the Adverse Event eCRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.2 Subject demographics/other baseline characteristics

Subject demographic and BSL characteristic data to be collected on all subjects and recorded in the eCRF include:

- Date of birth, age, sex, race, ethnicity and source of subject referral.
- Relevant PsA/Psoriasis and general medical history/current medical condition data until the start of study treatment, such as date of diagnosis of PsA/Psoriasis, previous PsA/Psoriasis therapies with the status of TNFα inhibitor naïve or IR, cardiovascular medical history, smoking history and surgical sterilization for females if applicable.

Whenever possible, diagnoses and not symptoms will be recorded.

6.3 Treatment exposure and compliance

All dates and times of study treatment administration will be recorded on the appropriate Dosage Administration Record eCRF page.

Drugs administered prior to start of treatment and other drugs/procedures continuing or started during the study treatment period will be entered in the Prior/Concomitant medications or Significant non-drug therapies eCRF page.

Compliance is expected to be 100%, unless temporary interruption is needed for safety reasons as described in (Section 5.5.5). Compliance will also be assessed by a Novartis monitor using information provided by the authorized site personnel.

6.4 Efficacy

The efficacy outcome measures used in this study are the standard measures used across all PsA trials and required for filing.

1. American College of Rheumatology (ACR) 20, 50 and 70 responses
   - Swollen Joint Count (SJC)/Tender Joint Count (TJC)
   - Patient's global assessment of disease activity (VAS)
   - Physician's global assessment of disease activity (VAS)
   - Patient's assessment of PsA pain intensity (VAS)
   - Health Assessment Questionnaire – Disability Index (HAQ-DI©)
   - high sensitivity C-Reactive Protein (hsCRP) and Erythrocyte Sedimentation Rate (ESR)
2. Progression of structural damage by X-ray (hands/wrists and feet) – van der Heijde mTSS and subscores (erosion and joint space narrowing score)

[redacted]

4. Disease Activity Score (DAS28)

[redacted]

8. [redacted] Dactylitis [redacted]
9. [redacted] Enthesitis [redacted]
10. Psoriasis Area and Severity Index (PASI)

[redacted]

All efficacy assessments should be performed prior to administration of study treatment.

Details relating to the administration of all PROs are provided in Appendix 2.

6.4.1 American College of Rheumatology (ACR) response

The ACR response (Appendix 3) will be used to determine efficacy (Felson et al 1995). A subject is defined as e.g. an ACR20 responder if, and only if, the following three conditions hold:

1. they have a ≥ 20% improvement in the number of tender joints (based on 78 joints)
2. they have a ≥ 20% improvement in the number of swollen joints (based on 76 joints)
3. they have a ≥ 20% improvement in three of the following five domains:
   - Patient's global assessment of disease activity (measured on a VAS scale, 0-100)
   - Physician's global assessment of disease activity (measured on a VAS scale, 0-100)
   - Patient's assessment of PsA pain (measured on a VAS scale, 0-100)
   - Health Assessment Questionnaire – Disability Index (HAQ-DI©) score
   - Acute phase reactant (hsCRP or ESR)

ACR50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.

ACR70 = 70% improvement in at least 3 of the 5 measures and 70% improvement in the swollen and tender joint count.

The ACR response is to be assessed at the visits/time points shown in Table 6-1 and Table 6-2.

6.4.1.1 Tender 78 joint count and swollen 76 joint count

Joint counts will be performed by the independent assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

The 78 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 2 first carpometacarpal, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hip, 2 knee, 2 talo-tibial, 2 mid-tarsal, 10 metatarsophalangeal, 10 proximal interphalangeal, and 8 distal interphalangeal joints of the feet. All of these except for the hips are assessed for swelling. Joint tenderness and swelling are to be graded present (1) or absent (0). Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count. Dactylitis of a digit in the foot or hand counts as one tender and swollen joint.

Data is recorded for tender and swollen joints (right or left side), i.e. a box (yes, no or not applicable) needs to be ticked for all joints.

6.4.1.2 Patient's assessment of PsA pain

The patient's assessment of pain will be performed using 100 mm visual analog scale (VAS) ranging from 'no pain' to 'unbearable pain' after the question '*Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today'*.

6.4.1.3 Patient's global assessment of disease activity

The patient's global assessment of disease activity will be performed using 100 mm visual analog scale (VAS) ranging from 'very good' to 'very poor' after the question 'Considering all the ways Psoriatic Arthritis affects you, p*lease indicate with a vertical mark (|) through the horizontal line how well you are today'*.

6.4.1.4 Physician's global assessment of disease activity

The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question *'Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today'*. To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that subject.

6.4.1.5 Health Assessment Questionnaire – Disability Index (HAQ- DI)

The HAQ-DI© was developed by Stanford University and is one of the most widely used measures to assess the long-term influence of chronic disease on a subject's level of functional ability and activity restriction. The disability assessment component of the HAQ, the HAQ-DI©, assesses a subject's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. There are 20 questions in eight categories of functioning including dressing, rising, eating, walking, hygiene, reach, grip, and usual activities. The stem of each item asks over the past week "Are you able to …" perform a particular task. Each item is scored on a 4-point scale from 0 to 3, representing normal (normal, no difficulty [0]), some difficulty (1), much difficulty (2), and unable to do (3).

The purpose of the HAQ-DI© in this study is to assess the functional ability of subjects with PsA.

6.4.1.6 High Sensitivity C-reactive protein (hsCRP)

Blood for this assessment will be obtained in order to identify the presence of inflammation, to determine its severity, and to monitor response to treatment.

Since the results of this test may unblind study personnel, results from the central lab will be provided for SCR and BSL only. The hsCRP results from samples collected during the treatment period will be revealed following database lock only.

6.4.1.7 Erythrocyte sedimentation rate (ESR)

Blood for ESR, which is helpful in diagnosing inflammatory diseases and is used to monitor disease activity and response to therapy, will be obtained at scheduled visits as indicated in Table 6-1 and Table 6-2.

6.4.2 Radiographic assessments

Separate radiographs of each hand/wrist (PA) and each foot (AP) will be taken at BSL, Week 16/24, 52, and 104. Bone erosion, joint space narrowing (JSN), and total radiographic scores will be determined using a PsA modified van der Heijde-Sharp (vdH-S) scoring method (van der Heijde et al 2005) that includes the second through fifth distal interphalangeal (DIP) joints of each hand. Erosions (0–5 in the hands and 0–10 in the feet) and JSN (0–4) will be graded separately in six wrist joints, all metacarpal phalangeal, proximal interphalangeal and DIP joints of each hand, and the first interphalangeal joint and all metatarsal phalangeal joints for each foot. The total radiographic score (hands and feet combined) ranges from 0 to 528, with higher scores indicating more articular damage. The maximum total erosion score is 320. The maximum total JSN score is 208.

The change in the Van der Heijde modified Sharp score is calculated against the BSL value. Radiologists will be trained on the X-ray acquisition and further details will be provided in a manual for the radiologists, e.g. joint placement and beam positioning.

In case of analogue X-rays films, the original film will be sent to the central reading CRO and will undergo quality control and will be digitized. Standard film and cassettes will be provided

to all centers that do not produce digital X-rays. In case of digital equipment, sites need to confirm minimum requirements with the imaging CROs Digital X-rays will be transferred electronically.

In case of insufficient quality, the center will be advised and trained on any quality issues prior to the repeat X-ray and to keep any repeat X-rays to a minimum.

Subjects who are non-responder at Week 16 (not achieving a ≥20% improvement from baseline in both TJC and SJC) will have their hands/wrists and feet X-rays taken at this visit (Week 16) and at Week 24 visit. Subjects who are responder at Week 16 (≥20% improvement from baseline in both tender and swollen joint counts) will have their hands/wrists and feet X-rays taken at Week 24.

Subjects who discontinue study treatment before the end of the trial, hands/wrists and feet X-rays will be taken at the time of study treatment discontinuation. However, if the radiograph performed at time of early discontinuation of study treatment is less than 60 days from a prior X-ray, it does not need to be performed except for Week 16 non-responders where a 30 day time period will apply between Weeks 16 and 24. Likewise, if a scheduled X-ray at Week 24, 52, or 104 is scheduled less than 60 days after any prior hands/wrists and feet X-rays, it does not need to be performed, except for Week 16 non-responders where a 30-day time period will apply between weeks 16 and 24..

The readings of the X-rays and the scoring will be performed centrally. Complete X-ray procedures will be defined in an Imaging Manual provided to the centers by an Imaging CRO designated by Novartis.

[redacted]

6.4.4 DAS28 [redacted]

The DAS28 is a measure of disease activity based on Swollen and Tender Joint Counts, ESR or CRP and the Patient Global Assessment of Disease Activity. A DAS28 score > 5.1 implies active disease, ≤ 3.2 low disease activity, and < 2.6 remission. [redacted]

[redacted]

[redacted]

Dactylitis count

The dactylitis count is the number of fingers and toes with dactylitis, with a range of 0-20.

Presence of dactylitis

If dactylitis is present with any finger or toe, the subject is counted as a subject with dactylitis.

[redacted]

Presence of enthesitis

If enthesitis is present with any of the 6 sites, the subject is counted as a subject with enthesitis.

6.4.9 Psoriasis Area and Severity Index (PASI)

The PASI assesses the extent of psoriasis on four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness. A PASI score (Fredriksson and Pettersson 1978, Weisman et al 2003, Gottlieb et al 2005) will be derived as indicated in Table 6-3.

The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details help the assessment:

- The neck is assessed as part of the head.
- The axillae and groin are assessed as part of the trunk.
- The buttocks are assessed as part of the lower limbs.

When scoring the severity of erythema, scales should not be removed.

Table 6-3 The PASI scoring system

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area%, A)*
Head (H)†	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0-< 10% 2 = 10-<30% 3 = 30-<50% 4 = 50-<70% 5 = 70-<90% 6 = 90-100%
Trunk (T)‡	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0-< 10% 2 = 10-<30% 3 = 30-<50% 4 = 50-<70% 5 = 70-<90% 6 = 90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0-< 10% 2 = 10-<30% 3 = 30-<50% 4 = 50-<70% 5 = 70-<90% 6 = 90-100%
Lower limbs (L)§	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0-< 10% 2 = 10-<30% 3 = 30-<50% 4 = 50-<70% 5 = 70-<90% 6 = 90-100%

* Percentage (not score) of body region (not whole body) affected will be entered in the CRF

† Neck is assessed as part of the Head (H) body region.

‡ Axillae and groin are assessed as part of the Trunk (T) body region.

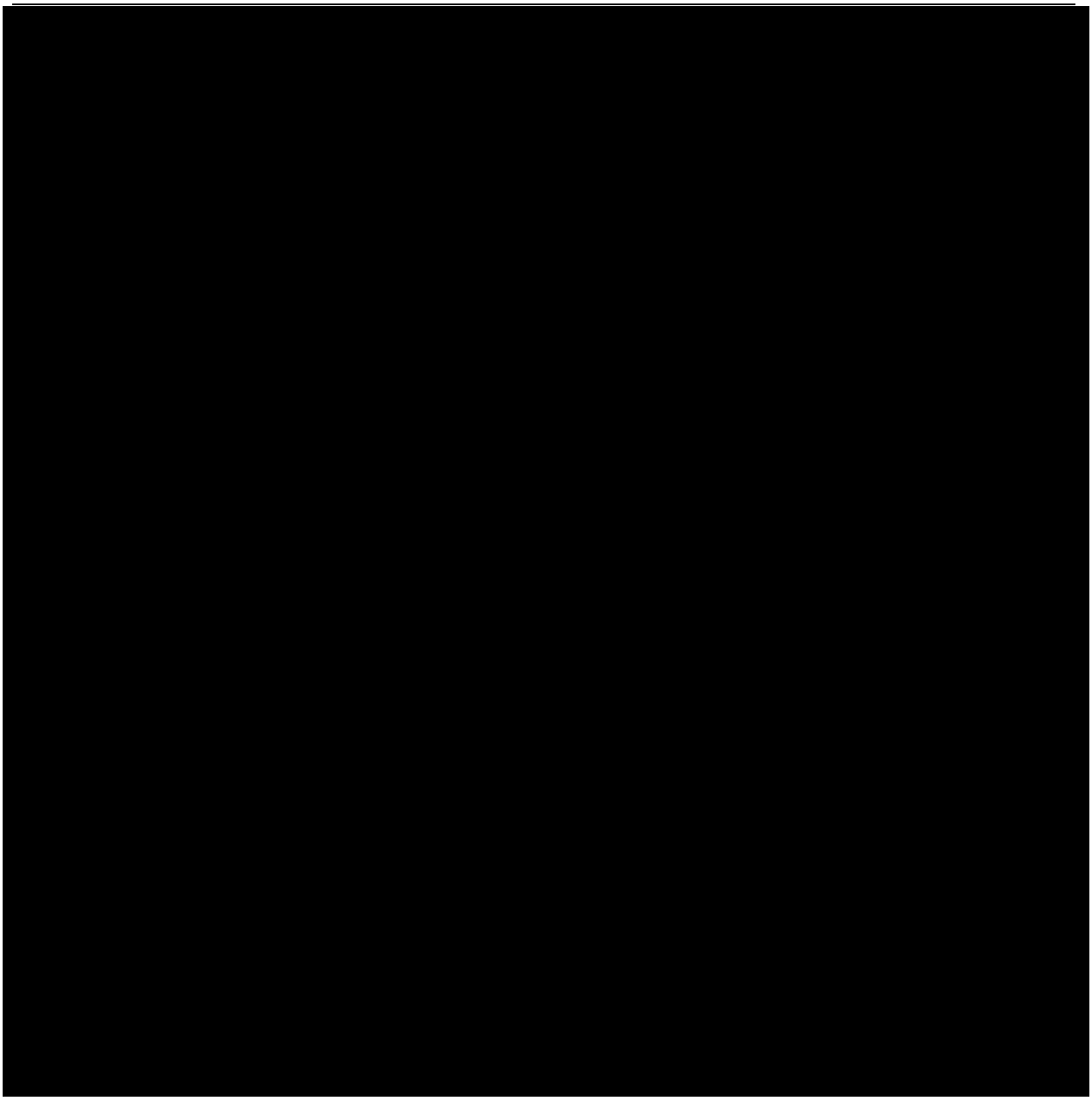
§ Buttocks are assessed as part of the Lower limbs (L) body region.

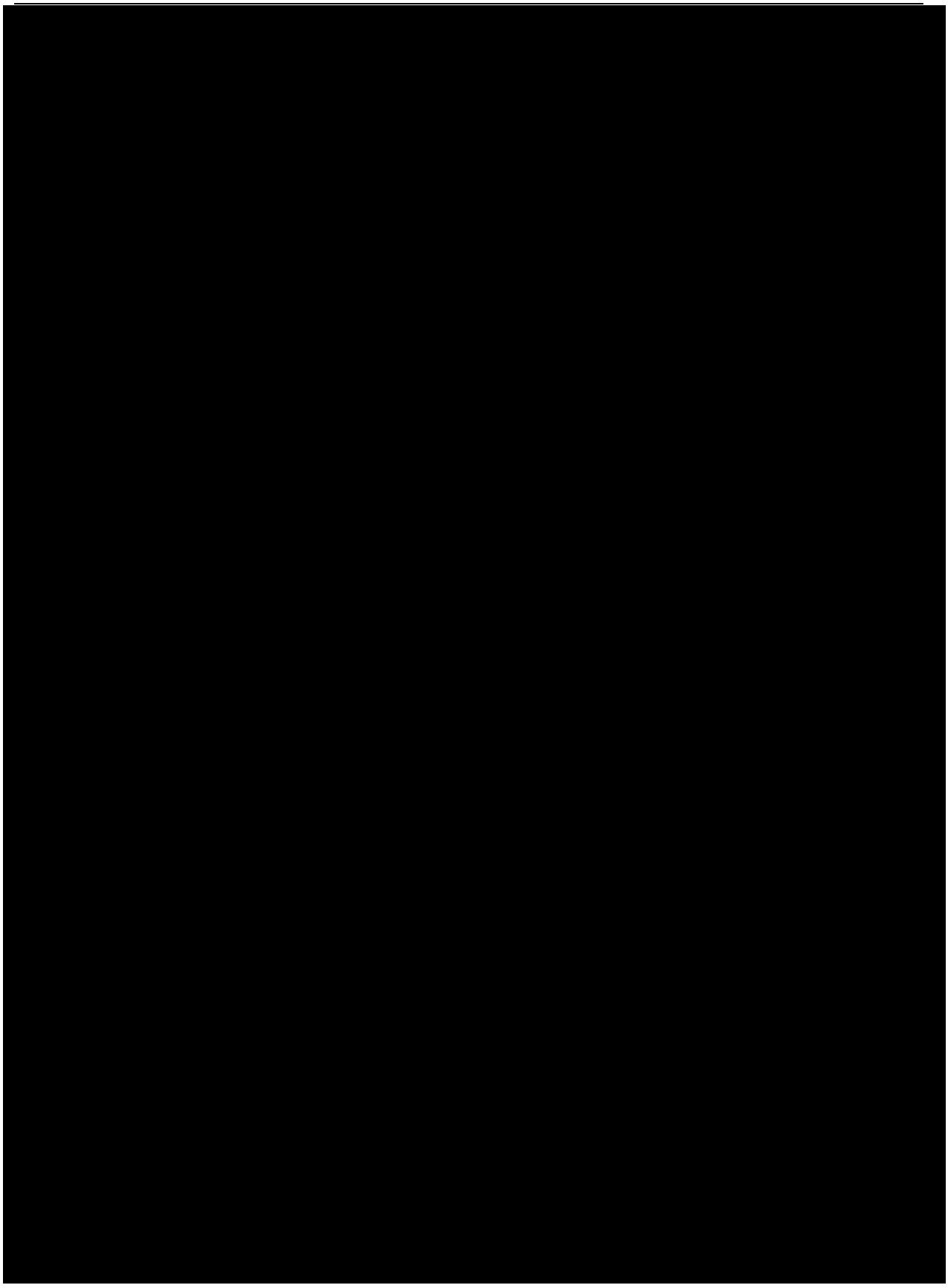
The head and neck, upper limbs, trunk and lower limbs correspond to approximately 10%, 20%, 30% and 40% of the body surface area, respectively; the PASI score is calculated using the following formula:

$$PASI = 0.1(E_H+I_H+D_H)A_H + 0.2(E_U+I_U+D_U)A_U + 0.3(E_T+I_T+D_T)A_T + 0.4(E_L+I_L+D_L)A_L$$

where E = erythema; I = induration; D = desquamation; A = area; H = Head; U = Upper limbs; T = Trunk; and L = Lower limbs

PASI scores can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.0. The investigator is responsible for collecting the components or scoring signs and total regional area. More information is provided in Appendix 5.





[redacted]

6.4.13 Appropriateness of efficacy assessments

The efficacy outcome measures used in this study are the standard measures used across many PsA trials and they are required for regulatory filing.

6.5 Safety

Evaluation of all AEs and SAEs including injection site reactions, electrocardiograms (ECGs), physical examination, vital signs and laboratory assessments, [redacted]

All blood draws and safety assessments should be done prior to study treatment administration. Appropriate safety assessments (e.g. evaluation of AEs and SAEs including injection site reactions) should be repeated after the dose is administered.

- Evaluation of AE/ SAE's
- Physical examination
- Vital signs
- Height and weight
- QuantiFERON TB-Gold test or PPD skin test
- Electrocardiogram
- Local tolerability (Injection site reactions)
- Laboratory evaluations (Hematology, Clinical Chemistry, Lipid Panel, Urinalysis)
- Pregnancy and assessment of fertility
- Tolerability of secukinumab
- [redacted]

6.5.1 Physical examination

The physical examination will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological system.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present before signing the ICF must be included in the relevant medical history eCRF. Significant findings made after signing the ICF which meet the definition of an AE must be recorded in the Adverse Event eCRF.

6.5.2 Vital signs

This will include blood pressure and pulse rate measurements after 5 minutes rest in sitting position. If possible, vital signs assessments should be performed by the same study site staff member using the same validated device throughout the study.

6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing but without shoes) will be measured.

If possible, body weight assessments should be performed by the same study site staff member using the same scale throughout the study.

6.5.4 QuantiFERON TB-Gold test or PPD skin test

Either a QuantiFERON TB-Gold test **or** a PPD skin test must be performed at SCR. Subjects with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active tuberculosis, or if presence of latent tuberculosis is established then treatment according to local country guidelines must have been initiated.

6.5.4.1 QuantiFERON TB-Gold test

A QuantiFERON TB-Gold test is to be performed at the second SCR visit and the results to be known prior to randomization to determine the subject's eligibility for the trial. The test will be used to screen the subject population for latent tuberculosis infection.

The test will be analyzed by the central laboratory. Details on the collection, processing and shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual.

6.5.4.2 PPD skin test

A PPD skin test is to be performed at SCR and read before randomization to determine the subject's eligibility for the trial. The test dose is bioequivalent to 5 tuberculin units of standard PPD injected intradermally, usually into the volar surface of the forearm. The site is cleaned and the PPD extract is then injected into the most superficial layer under the skin. If given correctly, the injection should raise a small wheal of about 5 mm, which resolves within 10-15 minutes.

Because the reaction (induration) will take 48-72 hours to develop, the subjects must return to the investigators' site within that time for a proper evaluation of the injection site. This will determine whether the subject has had a significant reaction to the PPD test. A reaction is measured in millimeters of induration (hard swelling) at the site. A PPD skin induration ≥5 mm (or according to local practice/guidelines) is interpreted as a positive result.

6.5.5 Laboratory evaluations

A central laboratory will be used for analysis of all specimens listed below (except urinalysis). Details on the collection, shipment of samples and reporting of results by the central laboratory are provided in the laboratory manual. For the identification of clinically notable values, see Appendix 7 and Appendix 8. All subjects with laboratory tests containing clinically significant abnormal values are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined.

6.5.5.1 Hematology

Hemoglobin, platelet, red blood cell (RBC), white blood cell (WBC) and differential white blood cell counts will be measured at scheduled visits.

6.5.5.2 Clinical chemistry

Serum chemistries will include glucose, urea, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), GGT, alkaline phosphatase, sodium, potassium, bicarbonate, calcium, phosphorous, total protein, albumin, and uric acid.

6.5.5.3 Urinalysis

Dipsticks will be provided by the central laboratory to the sites for local urinalysis assessments. The urinalysis results for standard parameters such as protein, glucose, blood and WBCs will be recorded in the appropriate eCRF page.

6.5.5.4 Lipid panel

A lipid profile including High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), cholesterol and triglycerides will be measured from a fasting blood sample.

6.5.5.5 Cardiovascular panel

A cardiovascular profile including lipoprotein (a), apolipoprotein B, apolipoprotein A-1, and adiponectin will be measured from a blood sample.

6.5.6 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed as indicated in Table 6-1 and Table 6-2. All ECGs must be performed on the ECG machines provided for the study.

All ECGs will be independently reviewed. Instructions for the collection and transmission of the ECGs to the independent reviewer will be provided in the ECG investigator manual.

Clinically relevant abnormalities should be recorded on the relevant medical history/Current medical conditions eCRF page for the BSL ECG.

Clinically relevant abnormalities noted after the BSL ECG should be reported as AE (see Section 7).

6.5.7 Pregnancy and assessments of fertility

Secukinumab must not be given to pregnant women; therefore effective methods of birth control must be used for women of child-bearing potential (see exclusion criteria definitions, Section 4.2).

A serum β-hCG test will be performed in all women at SCR. All women who are not surgically sterile or post-menopausal (as defined in Section 4.2) at SCR will have local urine pregnancy tests as indicated in Table 6-1 and Table 6-2. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If positive, the subject must be discontinued from the trial.

6.5.8 Tolerability of secukinumab

Tolerability will be assessed by AEs, laboratory values, injection site reaction and immunogenicity.

6.5.9 Additional parameters

Blood will be obtained at the first SCR visit (Visit 1) for anti-CCP antibodies and the Rheumatoid Factor (RF) assessment. Antinuclear antibody (ANA) and anti-double stranded deoxyribonucleic acid antibody (anti-dsDNA) antibodies will also be assessed at visits/time points indicated in Table 6-1 and Table 6-2.

6.5.11 Appropriateness of safety measurements

The safety measures used in this study are reliable and relevant standard measures for a biologic in PsA. A chest X-ray or MRI at SCR (or within 3 months prior to SCR) is performed to rule out the presence of a pulmonary malignancy of infectious process in particular tuberculosis.

The radiation exposure that results from these X-ray measurements is not necessary for medical care but is intended for research purposes only. The total amount of radiation from all X-ray measurements performed in this study (1 safety chest X-ray, 4 X-rays of hands/wrists and feet) is estimated to be around 1 mS over 104 weeks, and is approximately equivalent to a uniform whole body exposure of 26 weeks of exposure to natural background radiation. For effective radiation doses under 3 mS (300 mrem), the risk is considered to be minimal. Therefore, the radiation exposure in this study involves minimal risk and is necessary to ensure reliable safety measures before the treatment with a biologic.

The safety assessments selected are standard and adequate for this indication/subject population.

6.6 Other assessments

The other assessments planned for the study are:

- Quality of Life questionnaires/ Patient reported outcomes (PROs)
- [redacted]
- [redacted]

6.6.1 Resource utilization

No measures of Healthcare Resource Utilization (RU) will be collected in the study.

[redacted]

[redacted]

[redacted]

[redacted]

6.6.5 Health-related quality of life

The impact of PsA on various aspects of subjects' health-related quality of life (HRQoL) will be assessed using the following validated instruments:

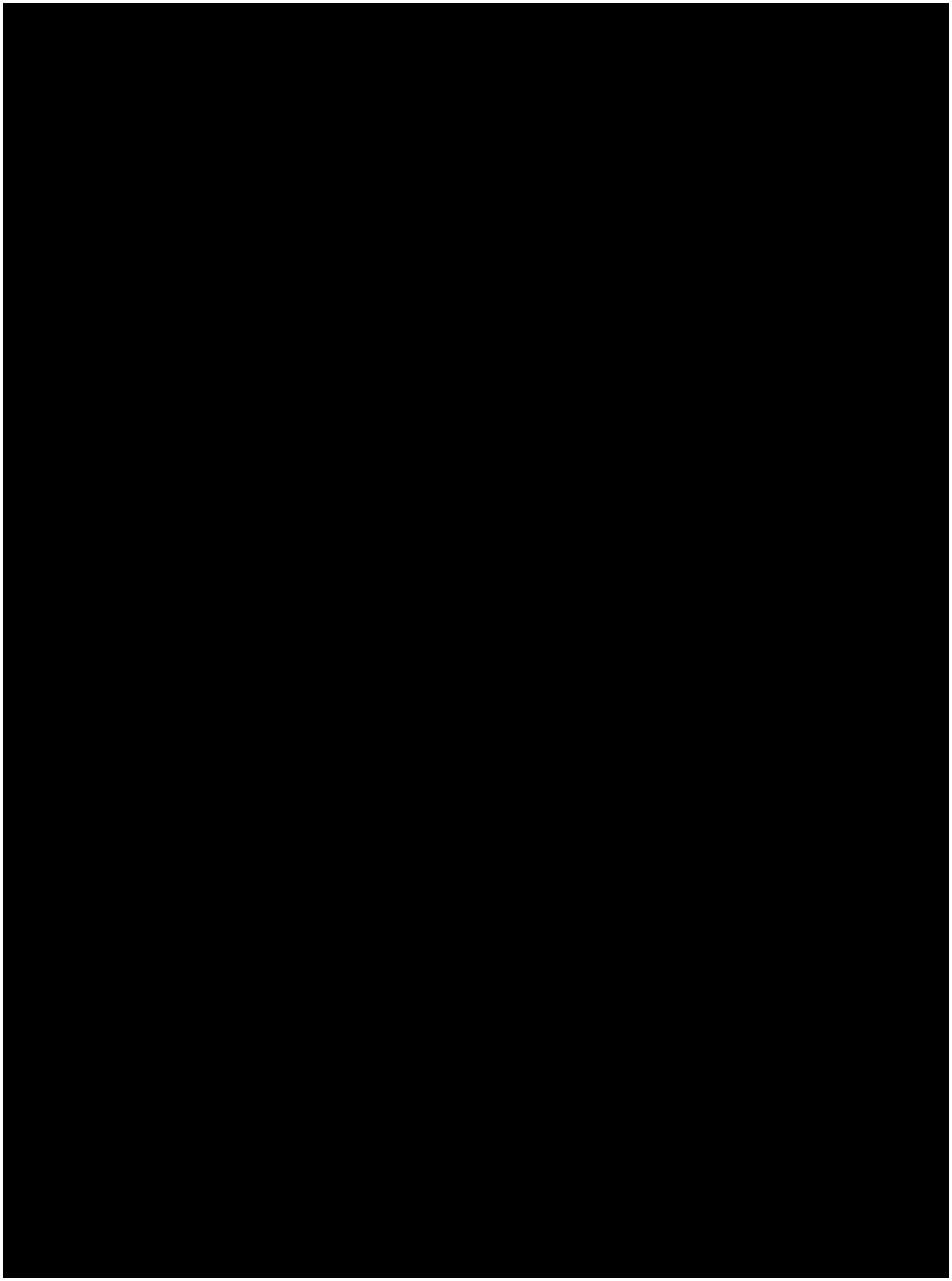
- HAQ-DI© (see Section 6.4.1.5)
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

All questionnaires will be completed at the defined visits/ time points listed in Table 6-1 and Table 6-2 prior to the subject seeing the investigator for any clinical assessment or evaluation. The questionnaires will be in the respondent's local language. The subject should be given sufficient instruction, space, time and privacy to complete the questionnaires. The study coordinator should check the questionnaires for completeness and encourage the subject to complete any missing responses.

Completed questionnaires should be reviewed and assessed by the investigator, before the clinical examination, for responses which may indicate potential AEs or SAEs. This assessment should be documented in the source records. If AEs or SAEs are confirmed the investigator should record the events as per instructions given in the relevant section of the protocol (see Section 7).

Guidelines for administering the PRO questionnaires can be found in Appendix 2.

[redacted]



7 Safety monitoring

7.1 Adverse events

An AE is any untoward medical occurrence (i.e., any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of AEs should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying AEs. Alert ranges for labs and other test abnormalities are included in Appendix 8.

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information.

- the severity grade
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
- its relationship to the study treatment (no/yes), its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
    - whether it constitutes a serious adverse event (SAE)
    - action taken regarding study treatment
    - whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
    - its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

An SAE is any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All AE's should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the AE should be recorded on the Adverse Event eCRF.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the IB or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new AE (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any AE (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to Drug Safety and Epidemiology (DS&E) as per Section 7.2.2.

7.2.2 Serious adverse event reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 12 weeks (84 days) after last administered dose of study treatment or 30 days after the subject has stopped study participation (whichever is later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE to each specific component of study treatment, (if study treatment consists of several components) complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / AEs have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to Table 19-1 in Appendix 7 for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event as defined in Table 19-1 of Appendix 7 should be followed up by the investigator or designated personal at the trial site as summarized below.

Detailed information is outlined in Table 19-2 in Appendix 7.

For the liver laboratory trigger:

- Repeating the LFT within the next week to confirm elevation or resolution.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the subject. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

For the liver events:

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and

the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Renal safety monitoring

There has been no safety signal for nephrotoxicity with secukinumab to date in over 8600 patients and healthy subjects exposed, and from a mechanism of action standpoint there is no known effect of blocking IL-17A on the kidney. All subjects with laboratory tests containing clinically significant abnormal values (see Appendix 8 for notable laboratory values) are to be followed until the values return to normal ranges or until a valid reason, other than treatment related AE, is defined. Standard renal function tests (blood urea nitrogen, serum creatinine) will be obtained at regular intervals, but special measures for renal safety monitoring are not planned.

7.5 Pregnancy reporting

All pre-menopausal women who are not surgically sterile will have a urine pregnancy test. A positive urine pregnancy test requires immediate interruption of study drug until serum β-hCG is performed and found to be negative.

To ensure subject safety, each pregnancy in a subject on study drug must be reported to Novartis/CRO within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments. Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis/CRO Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Novartis/CRO study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and good clinical practice (GCP) compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to GCP, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization, Additionally, a central analytics organization may analyze data & identify risks & trends for

site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the OC/RDC system. Designated investigator site staff will not be given access to the system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

ECG readings will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an IRT. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

8.4 Data Monitoring Committee

A Data Monitoring Committee is neither required nor planned for this study.

8.5 Adjudication Committee

An independent adjudication committee will be used to monitor specific safety events, including, but potentially not limited to clinically significant cardio- and cerebrovascular events. The events will be blindly reviewed and adjudicated as they occur during the conduct of the trial.

Details regarding the definition of AEs of special interest as well as the adjudication process will be available in the relevant secukinumab Adjudication Committee charter.

9 Data analysis

Summary statistics for continuous variables include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, and maximum. For binary or discrete variables the absolute number of subjects in each category and relative frequencies will be provided.

Unless otherwise specified, p-values will be presented as 2-sided p-values and the type I error rate (alpha) will be 5%.

Inferential efficacy comparisons with placebo will generally focus on the first 16-weeks of treatment except for radiographic assessment which will focus on the first 24-weeks of the treatment unless otherwise specified.

Efficacy and safety data for the placebo-controlled period (or the entire treatment period as appropriate) will be presented by treatment groups. Subjects may be included in more than one treatment group for some analyses (e.g. exposure-adjusted AEs over the entire treatment period).

Note that the treatment groups for a subject may differ depending on the time period of the analysis and whether one assesses the subject for efficacy or safety (see Section 9.1 for details).

Data may also be presented by a combination of the 'original' and 'switch' treatment groups. These treatment groups represent the treatment combinations the subjects experience over the course of the entire trial.

9.1 Analysis sets

The following analysis sets will be used in this trial:

Randomized set: The randomized set will be defined as all subjects who were randomized. Unless otherwise specified, mis-randomized subjects (mis-randomized in Interactive Voice Response (IVR)) will be excluded from the randomized set.

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IVR prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects are treated as screen failures.

Full analysis set (FAS): The FAS will be comprised of all subjects from the randomized set to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization, but with actual anti-TNF status.

Safety set: The safety set includes all subjects who took at least one dose of study treatment during the treatment period. Subjects will be evaluated according to treatment received.

9.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics

Summary statistics will be presented for continuous demographic and BSL characteristic variables for each treatment group and for all subjects in the randomized set. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group and all subjects.

The following demographic variables and BSL disease characteristics will be summarized by treatment groups:

- Gender, age, race, ethnicity, weight, height, and BMI
- TNFα history (naïve or inadequate responder), ACR components, number of prior biologic PsA therapies, dose of MTX or other DMARD at randomization.

Medical history

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

To establish a BSL level of cardiovascular risk, the number and percentage of subjects with pre-solicited cardiovascular risk factors will be summarized by treatment group. The number of cardiovascular risk factors that each subject has will also be summarized by treatment group. If it is unknown whether or not a subject currently or previously experienced a specific cardiovascular risk factor, it will be assumed that cardiovascular risk factor did not occur for that subject.

9.3 Treatments

Study treatment

The analysis of study treatment data will be based on the safety set. The number of active and placebo injections received will be presented by treatment group.

The duration of exposure to study treatment will also be summarized by treatment group. In addition, the number and percentage of subjects with cumulative exposure levels (e.g. any exposure, ≥ 1 week, ≥ 2 weeks, ≥ 3 weeks, ≥ 4 weeks, ≥ 8 weeks, etc.) will be presented.

Prior and concomitant medication

Prior and concomitant medications will be summarized in separate tables by treatment group. Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre- BSL and continued into the period where study treatment is administered.

Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of subjects receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

Significant prior and concomitant non-drug therapies and procedures will be summarized by primary system organ class and MedDRA preferred term.

The number and percentage of subjects receiving prior and concomitant PsA therapy will be presented by randomized treatment group as well as the reasons for stopping their therapies (primary lack of efficacy, secondary lack of efficacy, lack of tolerability, other).

9.4 Analysis of the primary variable(s)

Details of the testing strategy including primary and secondary endpoints are provided in Section 9.5.1

9.4.1 Variable(s)

The primary efficacy variable will be ACR20 response at Week 16. The analysis of the primary efficacy variable will be based on the FAS subjects. Primarily, CRP will be used instead of ESR to calculate ACR response; ESR will only be used in the event CRP is missing.

9.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis for ACR20 being tested is that there is no difference in the proportion of subjects fulfilling the ACR20 criteria at Week 16 in any of the secukinumab regimens vs. placebo regimen.

Let p_j denote the proportion of ACR20 responders at Week 16 for treatment regimens j, j=0, 1, 2, 3 where

- 0 corresponds to placebo regimen,
- 1 corresponds to secukinumab 150 mg PFS without loading,
- 2 corresponds to secukinumab 150 mg PFS with loading,
- 3 corresponds to secukinumab 300 mg PFS with loading,

In statistical terms, H_j: $p_j = p_0$, H_{Aj}: $p_j \neq p_0$, for the j^{th} secukinumab regimen, i.e.

H_1: secukinumab 150 mg s.c. without loading is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 16

H_2: secukinumab 150 mg s.c. with loading is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 16

H_3: secukinumab 300 mg s.c. with loading is not different to placebo regimen with respect to signs and symptoms (ACR20 response) at Week 16

The primary endpoint of ACR20 at Week 16 in the FAS will be evaluated using a logistic regression with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate. Odds ratios will be computed for comparisons of secukinumab regimens vs. placebo regimen utilizing the logistic regression model fitted.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data for ACR20 response and other binary efficacy variables (e.g. ACR50, ACR70, HAQ-DI© response, etc.) for data up to Week 24 will be handled as follows:

- Subjects who drop out of the trial for any reason will be considered non-responders from the time they drop out through Week 24.
- Subjects who do not have the required data to compute ACR response (i.e. tender and swollen joint counts and at least three of the five ACR core set variables) at BSL and at the specific time point will be classified as non-responders.

Continuous variables (e.g. ACR components, DAS, etc.) will be analyzed using a mixed-effects repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. For analyses of these parameters, if all post-BSL values are missing then these missing values will not be imputed and this subject will be removed from the analysis of the

corresponding variable, i.e. it might be that the number of subjects providing data to an analysis is smaller than the number of subjects in the FAS.

Data collected after Week 24 will generally be presented as 'observed case'; i.e. all available data for each time point will be included in the analyses.

In general, the handling of data for subjects who are rescued at Week 16 will be handled in the following fashion for comparisons with placebo at Week 20 and Week 24:

- For each binary endpoint, a subject will be consisted as a non-responder at Week 20/24 for that endpoint if the subject is a non-responder (including missing imputed non-responder) at Week 16. If a subject is a responder at Week 16, the actual value at Week 20/24 will be used (missing is considered as non-responder). This will be done for all treatment regimens in order to minimize bias.
- For continuous endpoints, the goal of the analyses would be to estimate what would have happened if the subjects had stayed on the original treatment. Thus, the data collected after the subject switches to secukinumab will be treated as missing for placebo subjects and will be analyzed using a MMRM which is valid under the missing at random (MAR) assumption. For secukinumab subjects, the actual values will be used in the analysis.

For comparisons between the active groups the rescue penalty will not be applied as the effect of rescuing is the same for both treatment groups (i.e. the subject continues to receive secukinumab 150 mg or 300 mg every 4 weeks).

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables are listed below. Secondary efficacy variables will be analyzed using the FAS population unless otherwise specified.

- Change from baseline in van der Heijde modified total Sharp score at Week 24
- PASI75 response at Week 16
- PASI90 response at Week 16
- ACR50 response at Week 16
- Change from baseline in HAQ-DI© score at Week 16
- Change from baseline in DAS28-CRP at Week 16
- Presence of enthesitis at Week 16
- Presence of dactylitis at Week 16

Testing strategy

- The following hypotheses will be included in the testing strategy, and type-I-errors will be set such that a family-wise type-I-error of 5% is kept:

Primary objectives (detailed in Section 9.4.2)

- H_1: secukinumab 300 mg is not different to placebo regimen with respect to ACR20 response at Week 16
- H_2: secukinumab 150 mg is not different to placebo regimen with respect to ACR20 response at Week 16
- H_3: secukinumab 150 mg No Load is not different to placebo regimen with respect to ACR20 response at Week 16

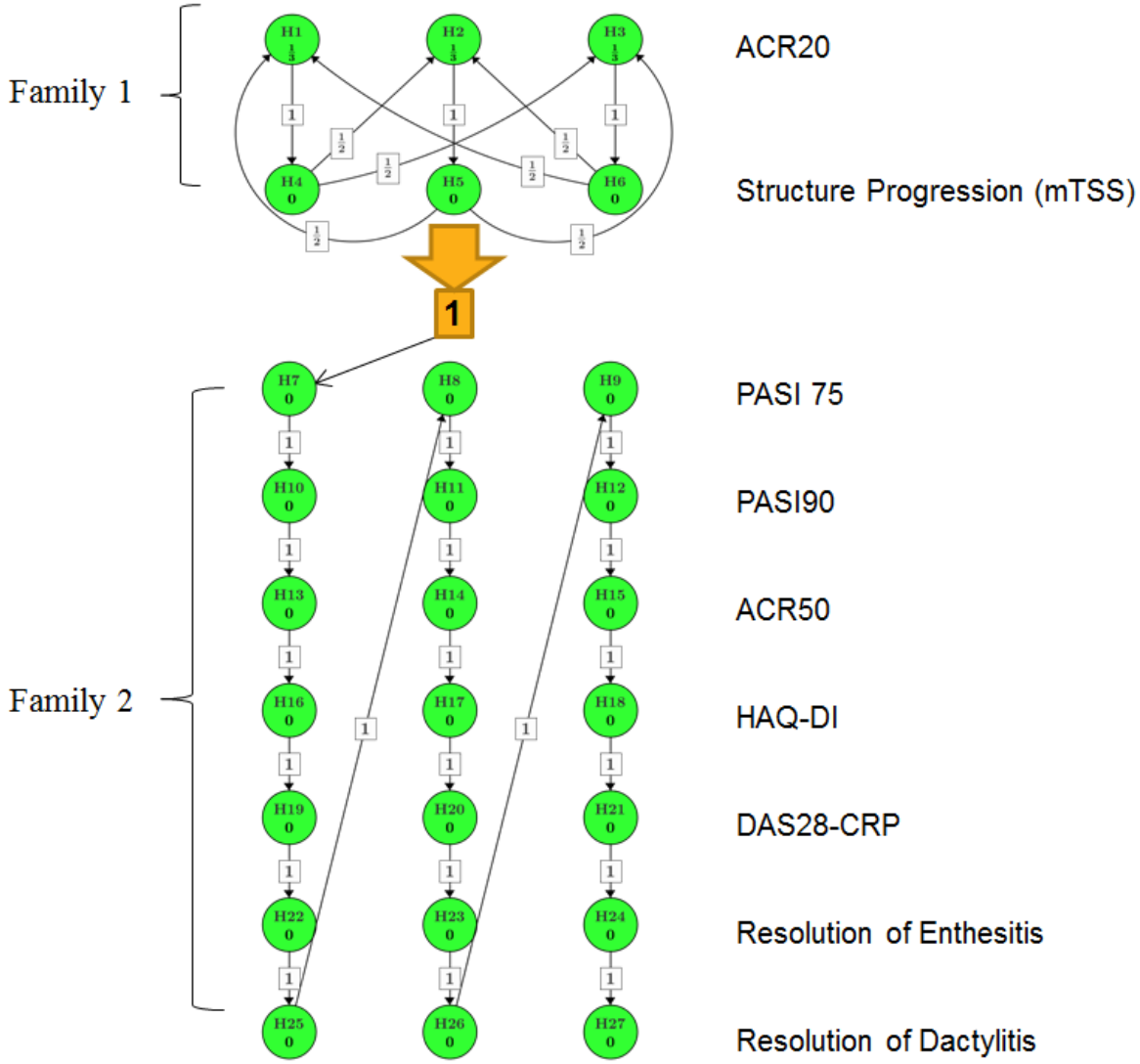
Secondary objectives:

- H_4: secukinumab 300 mg is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24
- H_5: secukinumab 150 mg is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24
- H_6: secukinumab 150 mg No Load is not different to placebo regimen with respect to structural damage (van der Heijde modified total Sharp score) at Week 24
- H_7: secukinumab 300 mg is not different to placebo regimen with respect to PASI75 response at Week 16 in the subset of subjects who have ≥3% skin involvement with psoriasis
- H_8: secukinumab 150 mg is not different to placebo regimen with respect to PASI75 response at Week 16 in the subset of subjects who have ≥3% skin involvement with psoriasis
- H_9: secukinumab 150 mg No Load is not different to placebo regimen with respect to PASI75 response at Week 16 in the subset of subjects who have ≥3% skin involvement with psoriasis
- H_{10}: secukinumab 300 mg is not different to placebo regimen with respect to PASI90 response at Week 16 in the subset of subjects who have ≥3% skin involvement with psoriasis

- H_{11}: secukinumab 150 mg is not different to placebo regimen with respect to PASI90 response at Week 16 in the subset of subjects who have ≥3% skin involvement with psoriasis
- H_{12}: secukinumab 150 mg No Load is not different to placebo regimen with respect to PASI90 response at Week 16 in the subset of subjects who have ≥3% skin involvement with psoriasis
- H_{13}: secukinumab 300 mg is not different to placebo regimen with respect to ACR50 response at Week 16
- H_{14}: secukinumab 150 mg is not different to placebo regimen with respect to ACR50 response at Week 16
- H_{15}: secukinumab 150 mg No Load is not different to placebo regimen with respect to ACR50 response at Week 16
- H_{16}: secukinumab 300 mg is not different to placebo regimen with respect to the change from baseline in HAQ-DI© at Week 16
- H_{17}: secukinumab 150 mg is not different to placebo regimen with respect to the change from baseline in HAQ-DI© at Week 16
- H_{18}: secukinumab 150 mg No Load is not different to placebo regimen with respect to the change from baseline in HAQ-DI© at Week 16
- H_{19}: secukinumab 300 mg is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at Week 16
- H_{20}: secukinumab 150 mg is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at Week 16
- H_{21}: secukinumab 150 mg No Load is not different to placebo regimen with respect to the change from baseline in DAS28-CRP at Week 16
- H_{22}: secukinumab 300 mg is not different to placebo regimen with respect to presence of enthesitis at Week 16 in the subset of subjects who have enthesitis at BSL
- H_{23}: secukinumab 150 mg is not different to placebo regimen with respect to presence of enthesitis at Week 16 in the subset of subjects who have enthesitis at BSL
- H_{24}: secukinumab 150 mg No Load is not different to placebo regimen with respect to presence of enthesitis at Week 16 in the subset of subjects who have enthesitis at BSL
- H_{25}: secukinumab 300 mg is not different to placebo regimen with respect to presence of dactylitis at Week 16 in the subset of subjects who have dactylitis at BSL
- H_{26}: secukinumab 150 mg is not different to placebo regimen with respect to presence of dactylitis at Week 16 in the subset of subjects who have dactylitis at BSL
- H_{27}: secukinumab 150 mg No Load is not different to placebo regimen with respect to presence of dactylitis at Week 16 in the subset of subjects who have dactylitis at BSL

The graphical approach of (Bretz et al 2009) for sequentially rejective testing procedures is used to illustrate the testing strategy:

Figure 9-1 Hierarchical testing strategy



The family-wise error will be set to α=5% and it will be controlled with the proposed hierarchical testing strategy. With this approach, the hypotheses will be separated into two families. The first family will include hypotheses of ACR20 at Week 16 and mTSS at Week 24 (H_1 through H_6). The Hypotheses of additional signs and symptoms (H_7 to H_{24}) will be the second family. The second family hypotheses will be tested only when all hypotheses in the first family have been rejected.

Each of the hypotheses (H_1, H_2 and H_3) for the primary objective (ACR20 at Week 16) for each secukinumab regimen vs. placebo will be tested simultaneously at α/3. Then based on the rejection of one or more (of H_1, H_2 and H_3), the mTSS at Week 24 endpoint will be tested hierarchically for each dose (through H_4, H_5 or H_6) at the level of α/3. If anyone is rejected, then half (1/2) of α/3 will be passed on to each of the other two hypotheses of ACR20 if they were not already rejected.

If H_1 to H_6 in the first family are all rejected, then AIN457 300 mg for all variables in the second family will be tested hierarchically at α starting from PASI75 (H_7). If all varaibles in AIN457 300 mg group are rejected then test AIN457 150 mg group and finally AIN 457 150 mg No Load group for all variables in hierarchy. Of note, in the description above, rejection of a hypothesis refers to rejection of the two-sided hypothesis; however the level of a rejected hypothesis is only passed on according to the graphical procedure for the test of another hypothesis if the treatment effect is in favor of secukinumab.

ACR50 at Week 16

Response at Week 16 to ACR50 in the FAS will be evaluated using a logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate.

Joint/bone structural damage at Week 24

The change at Week 24 from BSL van der Heijde total modified Sharp score will be evaluated using a non-parametric ANCOVA model with treatment regimen and randomization stratum (TNFα status – naïve or IR) as factors, and weight and BSL van der Heijde total modified Sharp score as covariates. For subjects either on placebo or active, who have a missing Sharp score at Week 24, linear extrapolation will be used to impute the value at Week 24 if at least two assessments exist before Week 24 (including baseline assessment).

For placebo subjects who meet the criteria for early escape at Week 16, they will be treated as missing for placebo treatment and linear extrapolation will be used to impute the value at Week 24. If BSL or all post- BSL total modified Sharp score/s is/are missing for a subject, the subject will be excluded from the analyses.

Sensitivity analysis will be performed with possibly valid missing data imputation methods including:

- Using all available Week 24 data for early escape for all subjects (placebo and active);
- LOCF instead of linear extrapolation;
- Multiple imputation and tipping point;
- Binary endpoint analysis (no disease progression defined as those subjects who have a change in mTSS at Week 24 relative to baseline <= 0.5) with logistic model:
    - LOCF;
    - Multiple imputation;
    - Tipping point.

Physical function (HAQ-DI©)

Between-treatment differences in the change in HAQ-DI© will be evaluated using a MMRM with treatment regimen, analysis visit and TNF-alpha inhibitor status as factors, and weight and BSL HAQ-DI© score as continuous covariates. Treatment by analysis visit and BSL by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for secukinumab

regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

Dactylitis at Week 16

Presence of dactylitis at Week 16 in the subset of subjects who have dactylitis at BSL will be evaluated using a logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate.

Enthesitis at Week 16

Presence of enthesitis at Week 16 in the subset of subjects who have enthesitis at BSL will be evaluated using a logistic regression model with treatment and randomization stratum (TNFα status –naïve or IR) as factors and weight as a covariate.

PASI75 and PASI90 response

PASI75 response and PASI90 at Week 16 will be evaluated for those subjects in whom the assessment occurred due to sufficient skin involvement (at least 3% BSA affected with psoriasis) (which is planned to be a subset of the FAS). These binary variables will be evaluated in the same fashion as ACR response, i.e. a logistic regression model with treatment and randomization strata as factors and weight as a covariate.

Changes in DAS28-CRP

Between-treatment differences in the change from baseline in DAS28-CRP will be compared by means of a MMRM with treatment regimen, analysis visit, and TNF-alpha inhibitor status as factors, and weight and BSL as continuous covariates. Treatment by analysis visit and BSL by analysis visit will be included as interaction terms in the model. An unstructured covariance structure will be assumed for this model. The significance of the treatment effects for secukinumab regimens at different analysis visits will be determined from the pairwise comparisons performed between secukinumab regimens and placebo at the appropriate analysis visits.

9.5.3 Safety variables

Adverse events

Treatment emergent AEs (events that started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized up to 12 weeks (84 days) after the last dose.

AEs will be summarized by presenting, for each treatment group, the number and percentage of subjects having any AE, having an AE in each primary system organ class and having each individual AE (preferred term). Summaries will also be presented for AEs by severity and for study treatment related AEs. If a subject reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a subject reported more than one AE within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable. SAEs will also be summarized.

These summaries may be presented separately by study periods.

As appropriate, the incidence of AEs will be presented per 100 subject years of exposure.

Separate summaries will be provided for death, SAE, other significant AEs leading to discontinuation and AEs leading to dose adjustment (including study treatment discontinuation).

A graphical display of relative frequencies within system organ classes and relative risks, as appropriate, will be presented.

When adjudication is required of major cardiovascular events, a summary of those types of events as reported by the investigator and confirmed by adjudication will be provided.

Laboratory data

The summary of laboratory evaluations will be presented for three groups of laboratory tests (hematology, serum chemistry and urinalysis). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both BSL and post- BSL.

For each parameter, the maximum change from baseline within each study period will be evaluated analogously.

In addition, shift tables will be provided for all parameters to compare a subject's BSL laboratory evaluation relative to the visit's observed value. For the shift tables, the normal laboratory ranges will be used to evaluate whether a particular laboratory test value was normal, low, or high for each visit value relative to whether or not the BSL value was normal, low, or high. These summaries will be presented by laboratory test and treatment group. Shifts will be presented by visit as well as for most extreme values post- BSL.

[redacted]

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post- BSL visit will be performed. These descriptive summaries will be presented by vital sign and treatment group. Change from baseline will only be summarized for subjects with both BSL and post- BSL values.

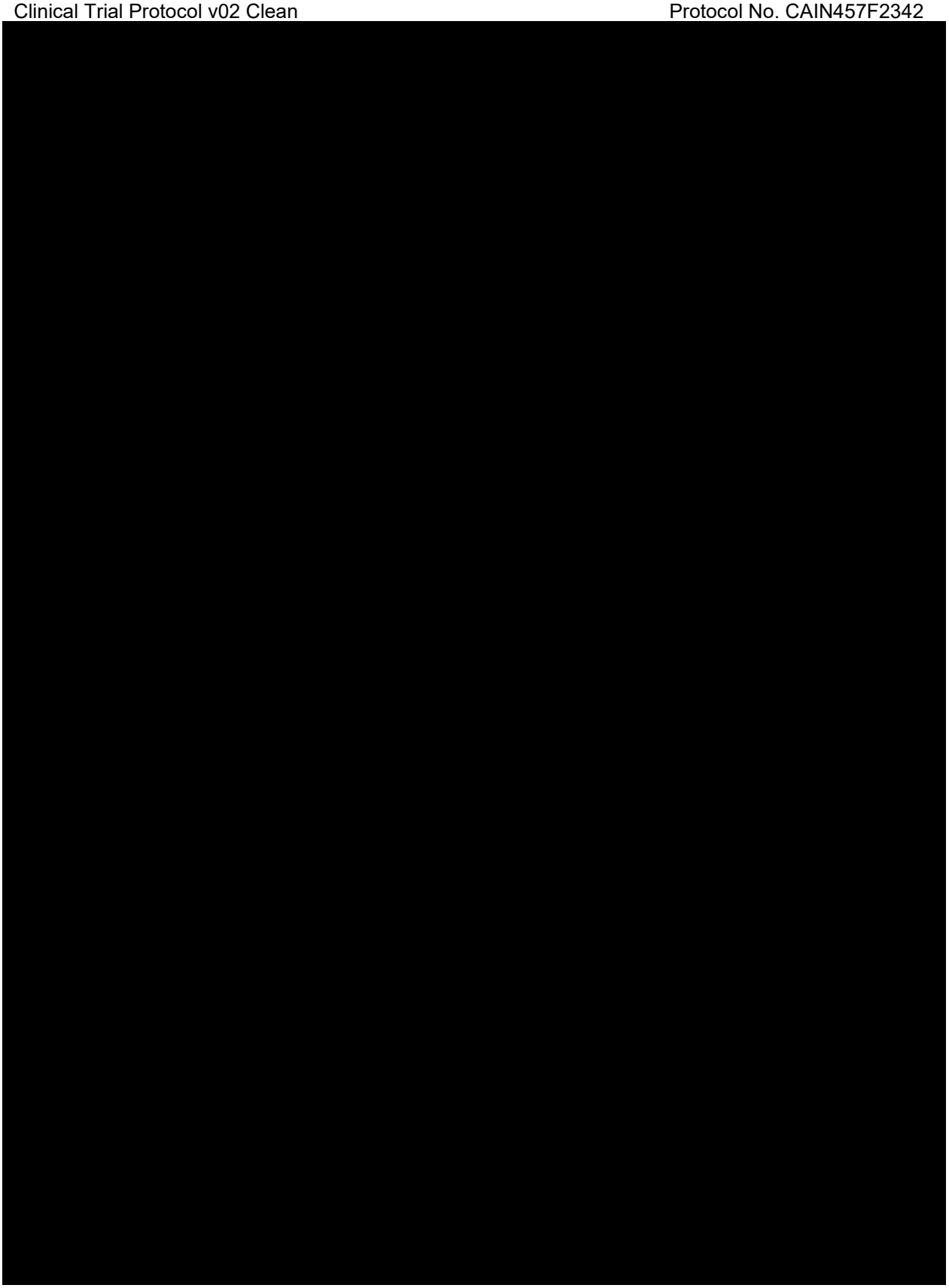
ECG

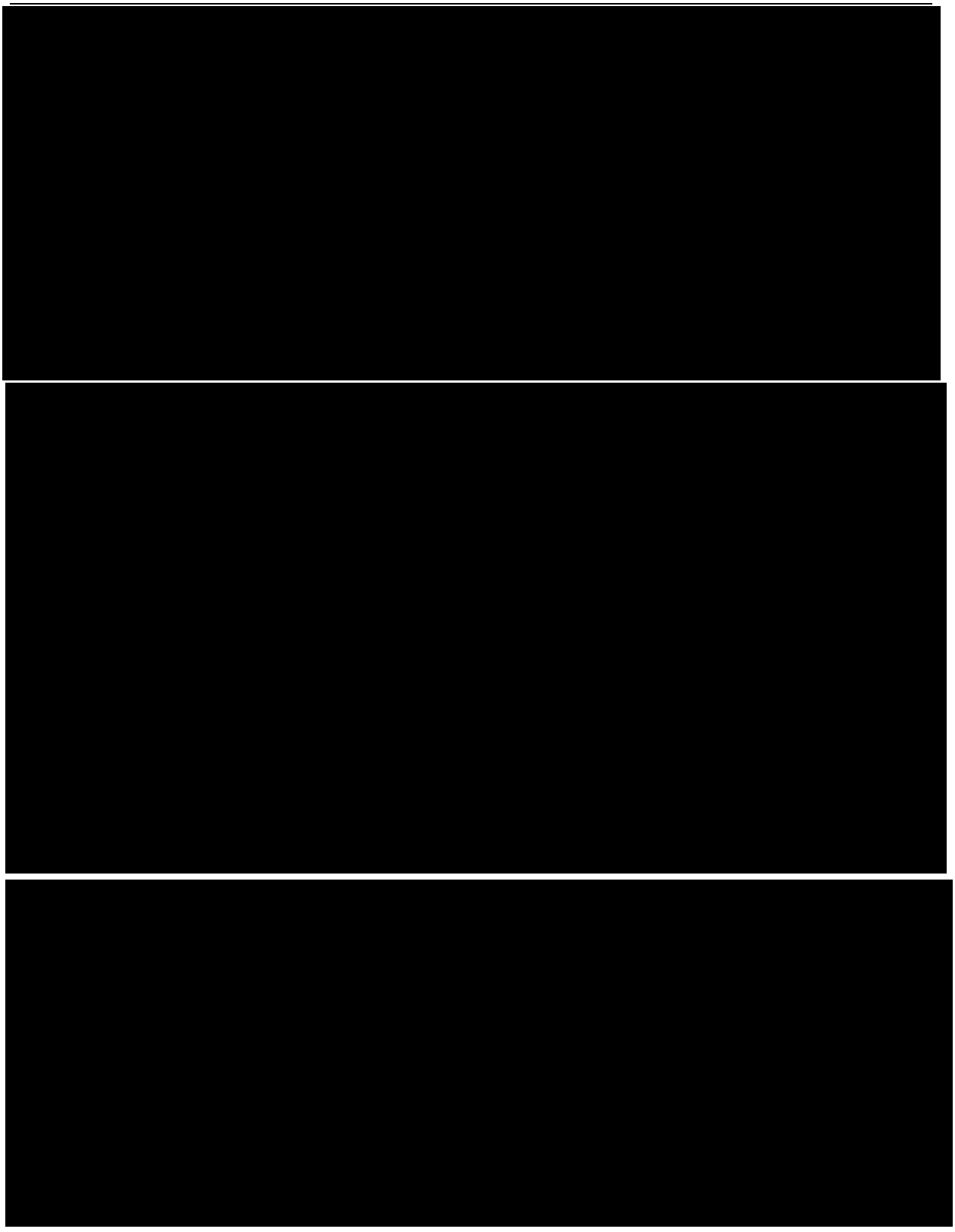
Summary statistics will be presented for ECG variables by visit and treatment group. Qualitative changes will be summarized.

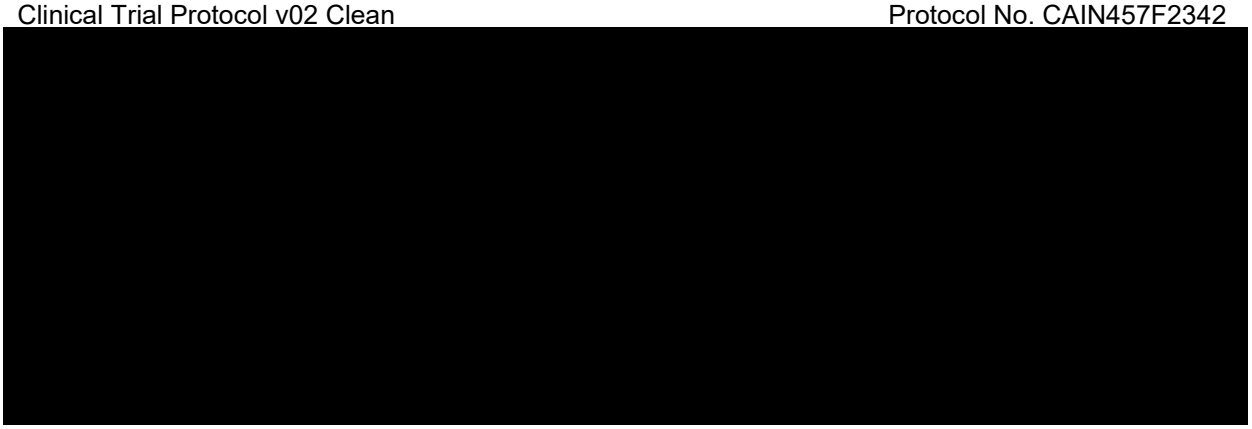
9.5.4 Health-related Quality of Life

[redacted] All Health-related Quality of Life will be evaluated based on FAS.

[redacted]







9.6 Interim analyses

The primary endpoint analysis will be performed in an interim analysis after all subjects have completed the Week 24 visit. The investigators, site personnel and monitors will continue to remain blinded to the original treatment assignment that each subject received at randomization until after the database lock for Week 52 analysis.

Subsequent to the primary endpoint analysis, additional analyses are planned after subjects have completed the Week 52 assessments and may be used for regulatory submission and/or publication purposes. The final analysis will be conducted after all subjects complete the study. Additional analyses may be performed to support interactions with health authorities, as necessary.

9.7 Sample size calculation

A 5% two-sided type I error rate will be used to control for type I error. Three secukinumab regimens will be tested versus placebo with respect to the primary endpoint (ACR20 response), thus the type-I-error will be split to 1.67% two-sided for each comparison. Sample sizes will be based on this type I error assumption. With an assumed placebo rate of 15% and secukinumab 51% (FUTURE 2), the study is over 99% powered to detect a treatment difference of ACR20 in the FAS population, assuming 220 subjects in a secukinumab treatment group, and 330 subjects in the placebo group (Fisher's exact test, nQuery 7.0). This power is applicable for all three dose regimens, as the sample size is driven by structural endpoint.

Power for secondary variables was calculated using a two-sided 1.67% type I error. With an assumed placebo rate of 7% and secukinumab 35% (FUTURE 2), the study is over 99% powered to detect a treatment difference of ACR50 in the full FAS population, assuming 220 subjects in a secukinumab treatment group, and 330 subjects in the placebo group (Fisher's exact test, nQuery 7.0).

For structural endpoint, historical data (FUTURE 1) showed a standard deviation of 1.132 on active treatment and 2.435 on placebo at Week 24, and a difference of 0.52. Using the above

assumptions, there is 83% power to show statistically significant differences assuming 220 subjects in a secukinumab group and 330 subjects in the placebo group (Satterthwaite t-test, nQuery 7.0).

A standard deviation of approximately 0.49 and a treatment difference of 0.17 has been observed for the change from baseline at Week 24 in HAQ-DI© (FUTURE 2). Using those assumptions, the study has approximately 94% power to detect a difference between secukinumab and placebo (Two group t-test, nQuery Advisor 7.0), assuming 220 subjects in a secukinumab treatment group and 330 subjects in the placebo group.

For the presence of dactylitis in the subset of subject who have dactylitis at BSL, with an assumed placebo rate of 85% and secukinumab 50% (FUTURE 2), there is about 99% power to show statistically significant difference between secukinumab (110) and placebo (165 subjects), assuming 50% subject have dactylitis at BSL (Fisher's exact test, nQuery 7.0).

For the presence of enthesitis in the subset of subject who have enthesitis at BSL, with an assumed placebo rate of 79% and secukinumab 58% (FUTURE 2), there is about 94% power to show statistically significant difference between secukinumab (132 subjects) and placebo (198 subjects), assuming 60% subjects have enthesitis at BSL (Fisher's exact test, nQuery 7.0).

With an assumed placebo rate of 16% and secukinumab 48% (FUTURE 2), the study is over 99% powered to detect a treatment difference of PASI75 in the FAS population, assuming 110 subjects in a secukinumab treatment group, and 165 subjects in the placebo group. It is assumed that about 50% of enrolled subjects have ≥3% skin involvement.

A difference of 0.62 and standard deviation of 1.04 has been observed for the change from baseline in DAS28-CRP (FUTURE 2). With these assumptions, the study has over 99% power to detect a difference between secukinumab and placebo (Two group t-test, nQuery Advisor 7.0), assuming 220 subjects in a secukinumab treatment group, and 330 subjects in the placebo group.

With an assumed placebo rate of 9% and secukinumab 33% (FUTURE 2), the study is over 99% powered to detect a treatment difference of PASI90 in the FAS population, assuming 110 subjects in a secukinumab treatment group, and 165 subjects in the placebo group. It is assumed that about 50% of enrolled subjects have ≥3% skin involvement.

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee

(IRB/IEC)-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study, and for minimum 16 weeks or longer if local label requires it (e.g. 20 weeks in EU) after the last dose. If there is any question that the subject will not reliably comply, they should not be entered in the study.

[redacted]

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report, the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 “Safety Monitoring” should be followed.

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13 Appendix 1: The classification criteria for psoriatic arthritis (CASPAR)

To meet the Classification of Psoriatic Arthritis (CASPAR) criteria for diagnosis of psoriatic arthritis according to (Taylor 2006), a subject must have inflammatory articular disease (joint, spine or entheseal) and at least 3 points from the following 5 categories:

1. Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.* (**2 points**)
   - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider. (**1 points**)
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report. (**1 points**)
2. Typical psoriatic nail dystrophy including onycholysis, pitting, and hyperkeratosis observed on current physical examination (**1 point**)
3. A negative test result for the presence of rheumatoid factor by any method except latex (**1 point**)
4. Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (**1 point**)
5. Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot (**1 point**)

Total score:

(The CASPAR criteria eCRF will autopopulate the total number of points of the CASPAR criteria met by the subject. If the total score ≥ 3, the subject meets CASPAR criteria for PsA diagnosis.)

* Current psoriasis is assigned a score of 2; all other features are assigned a score of 1

14 Appendix 2: Guidelines for administering the questionnaires for patient reported outcomes

Before trial start

Study coordinators should familiarize themselves with the PRO questionnaire(s) in the trial and identify any items where a patient's response might highlight issues of potential concern.

At BSL, BSA involvement with psoriasis should be determined before completing PRO questionnaire(s) to ensure that DLQI is completed only for patients who have BSA≥3%.

For example, one question in the SF-36 asks 'How much of the time in the past 4 weeks- have you felt downhearted and blue?' If a patient responds 'most or all of the time', then the study coordinator should inform the study investigator.

Before completion

1. Subjects should be provided with the correct questionnaire at the appropriate visits and in the appropriate language
2. Subjects should have adequate space and time to complete the forms
3. Patients should be provided with a firm writing surface (such as a table or a clip board)
4. Questionnaire should be administered before the clinical examination

During completion

1. Administrator may clarify the questions but should not influence the response
2. Only one response for each question
3. Also see "Addressing Problems and Concerns"

After completion

1. Check for completeness and not for content*
2. Data should be sent from the eCRF / electronic device
3. Data should be reviewed by Investigator for AEs

*However, any response which may directly impact or reflect the patient's medical condition (e.g. noting of depression) should be communicated by the study coordinator to the investigator).

Addressing Problems and Concerns

Occasionally a patient may have concerns or questions about the questionnaires administered. Guidance related to some of the most common concerns and questions are given below.

The patient does not want to complete the questionnaire(s)

Tell the patient that completion of the questionnaire(s) is voluntary. The goal is to better understand the physical, mental and social health problems of patients. Emphasize that such information is as important as any other medical information and that the questionnaire(s) is simple to complete. Suggest that the questionnaire(s) may be different from anything the

respondent has filled in the past. If the patient still declines, retrieve the questionnaires. Record the reason for the decline and thank the patient.

The patient is too ill or weak to complete the questionnaire(s)

In these instances, the coordinator may obtain patient responses by reading out loud each question, followed by the corresponding response categories, and entering the patient's response. No help should be provided to the patient by any person other than the designated study coordinator. The coordinator should not influence patient responses. The study coordinator cannot translate the question into simpler language and has to be read verbatim.

The patient wants someone else to complete the questionnaire(s)

In no case should the coordinator or anyone other than the patient provide responses to the questions. Unless specified in the study protocol, proxy data are *not* an acceptable substitute for patient self-report. Patients should be discouraged from asking a family member or friend for help in completing a questionnaire.

The patient does not want to finish completing the questionnaire(s)

If non-completion is a result of the patient having trouble understanding particular items, ask the patient to explain the difficulty. Re-read the question for them *verbatim* but do not rephrase the question. If the respondent is still unable to complete the questionnaire, accept it as incomplete. Thank the patient.

The patient is concerned that someone will look at his/her responses

Emphasize that all responses are to be kept confidential. Point out that their names do not appear anywhere on the questionnaire, so that their results will be linked with an ID number and not their name. Tell the patient that his/her answers will be pooled with other patients' answers and that they will be analyzed as a group rather than as individuals. Tell the patient that completed forms are not routinely shared with treating staff and that their responses will only be seen by you (to check for completeness) and by the investigator. Any response which may directly impact on or reflect their medical condition (*e.g.* noting of severe depression) will be communicated by the coordinator to the physician.

The patient asks the meaning of a question/item

While completing the questionnaire, some patients might ask the meaning of specific items so that they can better understand and respond. If this happens, assist the patient by rereading the question for them *verbatim.* If the patient asks to interpret the meaning of an item, do not try to explain it, but suggest that he/she use his/her own interpretation of the question. Patients should answer the questions based on what *they* think the questions mean.

A General Information about all questionnaire(s):

All questionnaires have to be completed by the patients in their local languages using an electronic device. The questionnaires should be completed by the patients in a quiet area free from disturbance, and before any visit assessments. Patients should receive no help from family members; if questions cannot be answered alone (due to problems with reading or

understanding), then the doctor or nurse should read the questions and record the patient's responses without influencing their answers. The information provided is strictly confidential and will be treated as such. If a patient has missed a question or given more than one response per question, then this should be brought to patient. Incomplete questions should not be accepted without first encouraging the patient to complete unanswered questions.

The investigator must complete the patient/visit information on the electronic device and ensure that the center number, patient's number and initials are identical to the CRF. As there are no source data for this questionnaire, the data queries will be restricted to patient/visit information.

15 Appendix 3: American College of Rheumatology (ACR) Measures and Criteria of Response

Number of tender joints

Seventy-eight joints (78) are scored as either tender or not tender: 8 distal interphalangeal, 10 proximal interphalangeal, 10 metacarpophalangeal and 2 first carpometacarpal joints of the hands, 8 distal interphalangeal, the 10 metatarsophalangeal and 10 proximal interphalangeal joints of the feet, the 2 wrists, 2 elbows, 2 shoulders, 2 acromioclavicular, 2 sternoclavicular, 2 temporomandibular, 2 hip, 2 knee, 2 talo-tibial, and 2 mid-tarsal joints.

Joint tenderness is to be scored present (1) or absent (0).

Number of swollen joints

Joints are to be scored as either swollen (1) or not swollen (0). The 76 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Patient's assessment of PsA pain

On a 100 mm non-anchored visual analog scale, from no pain to unbearable pain.

Patient's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity, after the question "Considering all the ways your arthritis affects you, draw a line on the scale for how well you are doing".

Physician's global assessment of disease activity

On a 100 mm non-anchored visual analog scale, from no arthritis activity to maximal arthritis activity.

Patient's assessment of physical function

Health Assessment Questionnaire – HAQ-DI©ACR20/50/70*

A patient will be considered as improved according the ACR20 criteria* if she/he has at least

20% improvement in

- the two following measures:
  - Tender joint count
  - Swollen joint count
- and at least 3 of the following 5 measures:
  - Patient's assessment of pain
  - Patient's global assessment of disease activity
  - Physician's global assessment of disease activity
  - Health Assessment Questionnaire (HAQ©) score
  - C-reactive protein (CRP)/Erythrocyte Sedimentation Rate (ESR).

ACR50 = 50% improvement in at least 3 of the 5 measures and 50% improvement in the swollen and tender joint count.

ACR70 = 70% improvement in at least 3 of the 5 measures and 70% improvement in the swollen and tender joint count.

Reference: (Felson et al 1995)

17 Appendix 5: The Psoriasis Area and Severity Index (PASI)

The PASI is a system used for assessing and grading the severity of psoriatic lesions and their response to therapy. The PASI produces a numeric score that can range from 0 to 72. The severity of disease is calculated as follows. In the PASI system, the body is divided into 4 regions: the head (h), trunk (t), upper extremities (u), and lower extremities (l), which account for 10%, 30%, 20% and 40% of the total BSA, respectively. Each of these areas is assessed separately for erythema, induration and desquamation (scaling), which are each rated on a scale of 0 to 4. The scoring system for the signs of the disease (erythema, induration, and desquamation (scaling)) are:

0 = none; 1= slight; 2 = moderate; 3 = severe; and 4 = very severe.

The scale for estimating the area of involvement for psoriatic lesions is outlined below.
0 = no involvement
1 = 1% to 9% involvement
2 = 10% to 29% involvement
3 = 30% to 49% involvement
4 = 50% to 69% involvement
5 = 70% to 89% involvement
6 = 90% to 100% involvement

To help with the area assessments, the following conventions should be noted:

- the neck is considered part of the head
- the axillae and groin are part of the trunk
- the buttocks are part of the lower extremities

The PASI formula is: PASI = 0.1 (Eh + Ih + Dh) Ah + 0.3 (Et +It+ Dt) At+ 0.2 (Eu + Iu + Du) Au+ 0.4 (El +II+ Dl) AI (where E= erythema, I = induration, D = desquamation and A = area)

Table 17-1 PASI Scoring Worksheet

		Head	Upper extremities	Trunk	Lower extremities
1.	Redness †				
2.	Thickness †				
3.	Scale †				
4.	Sum of rows 1, 2, and 3				
5.	Area score ‡				
6.	Score of row 4 x row 5 x the area multiplier	Row 4 x row 5 x 0.1	Row 4 x row 5 x 0.2	Row 4 x row 5 x 0.3	Row 4 x row 5 x 0.4
7.	Sum row 6 for each column for PASI score				

a. Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.
b. Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0=clear, 1-4=increasing severity).
c. Sum scores of erythema, thickness, and scale for each of the 4 area.

d. Generate a percentage for skin covered with psoriasis for each area and convert that to a 0-6 scale. ‡

e. Multiply score of item c above times item d above for each area and multiply that by 0.1, 0.2, 0.3 and 0.4 for head, arms, trunk, and legs, respectively.

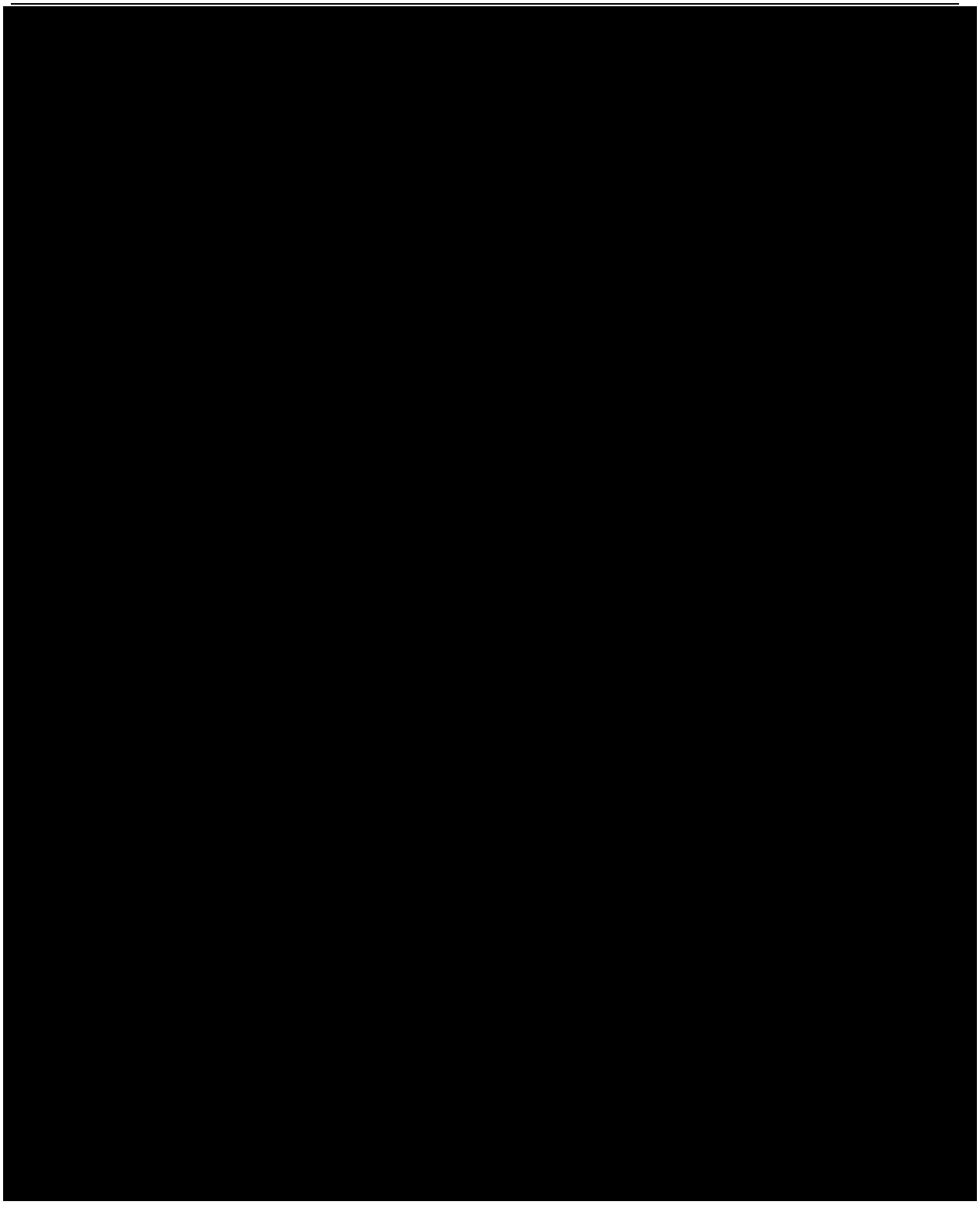
f. Add these scores to get the PASI score.

† Erythema, thickness, and scale are measured on a 0-4 scale (none, slight, mild, moderate, severe)

‡ Area scoring criteria (score: % involvement).

0: 0% (clear)
1: <10%
2: 10-<30%
3: 30-<50%
4: 50-<70%
5: 70-<90%
6: 90-100%

Derived from Feldman and Krueger,2005. Psoriasis assessment tool in clinical trials. Ann Rheum Dis; 64;ii65-ii68.



19 Appendix 7: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 19-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT / AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN ALP > 2 × ULN (in the absence of known bone pathology) TBL > 2 × ULN (in the absence of known Gilbert syndrome) ALT or AST > 3 × ULN and INR > 1.5 Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) Any clinical event of jaundice (or equivalent term) ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any adverse event potentially indicative of a liver toxicity *

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

Table 19-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	Discontinue the study drug immediately Hospitalize, if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	Repeat LFT within 48 hours If elevation persists, continue follow-up monitoring If elevation persists for *more than 2 weeks*, discontinue the study drug Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	Discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	Repeat LFT within 48 hours If elevation persists, establish causality Complete liver eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	Repeat LFT within the next week If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	Discontinue the study drug immediately Hospitalize the patient Establish causality Complete liver eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	Consider study drug interruption or discontinuation Hospitalization if clinically appropriate Establish causality Complete liver eCRF	Investigator discretion

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms

TBL: total bilirubin; ULN: upper limit of normal

[a] Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

[b] (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

20 Appendix 8: Clinically notable laboratory values

The following guidance will be used to define expanded limits and notable abnormalities of key laboratory outcomes.

Clinically notable values will be forwarded to Novartis in the same time as sent to the investigators. Any intervention based on these laboratory values should be discussed with Novartis personnel.

Laboratory variable	Notable criteria
Liver function and related variables	
SGOT (AST)	>3 x ULN
SGPT (ALT)	>3 x ULN
Bilirubin	>2 x ULN
Alkaline phosphatase	>2.5 x ULN
Renal function, metabolic and electrolyte variables	
Creatinine (serum)	>2 x ULN
Hematology variables	
Hemoglobin	20 g/L decrease from Baseline
Platelet count	<100 x 10^9/L
White blood cell count	<0.8 x LLN
Neutrophils	<0.9 x LLN